08/278,112

#47 DAC

PATENT
Attorney Docket No. 26649U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:
U.S. Patent No. 5,482,934

Issued: January 9, 1996

To: Jose Calatayud et al.

For: PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

From: Serial No.: 08/278,112

Filed: July 20, 1994

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner for Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Transmitted herewith is the application of ALTANA PHARMA AG for extension of the term of United States Patent No. 5,482,934 under 35 U.S.C. § 156, together with two duplicates of the papers thereof, and Check No. 3358 in the amount of $1,120.00, certified as such.

The Commissioner is hereby specifically authorized to charge any required fee deficiency under 37 CFR §§ 1.16 or 1.17, or credit any overpayment, to Deposit Account No. 14-0112 in connection with this matter. Two duplicates of this paper are enclosed.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Date: December 15, 2006

NATH & ASSOCIATES PLLC
112 S. West Street
Alexandria, VA 22314
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Gary M. Nath
Reg. No. 26,965
Joshua B. Goldberg
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PATENT
Attorney Docket No. 26649U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:
U.S. Patent No. 5,482,934

Issued: January 9, 1996

To: Jose Calatayud et al.

For: PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

From: Serial No.: 08/278,112

Filed: July 20, 1994

APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 5,482,934 UNDER 35 U.S.C. § 156

Honorable Commissioner for Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Your applicant, ALTANA PHARMA AG ("ALTANA"), a corporation existing under the laws of Germany and having a place of business at BYK-GULDEN-STRASSE 2, D-78467 Konstanz, Germany, represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 5,482,934, granted to JOSE CALATAYUD, JOSE R. CONDE, and MANUEL LUNA on the 9th day of January, 1996, for PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS, by virtue of assignments/and or name change documents recorded in the United States Patent and Trademark Office on the 6th day of August, 1991, at Reel

005791, Frame 0570; the 14th day of May, 1993, at Reel 006522, Frame 0565; the 19th day of March, 1993, at Reel 006467, Frame 0223; the 22nd day of March, 1993, at Reel 006464, Frame 0548, the 11th day of June, 1993, at Reel 006578, Frame 0579; the 5th day of August, 1998, at Reel 009367, Frame 0001; and the 7th day of April, 2003, at Reel 013922, Frame 0540, a copy of which assignments/and or name change documents are attached as Exhibit A; that Altana Pharma U.S., Inc. ("ALTANA U.S.") is a wholly-owned subsidiary of ALTANA PHARMA AG (through its wholly-owned affiliate Altana Pharma Asset Management GmbH); that ALTANA U.S. is the sponsor of New Drug Application ("NDA") No. 22-004 for OMNARIS™ (ciclesonide) Nasal Spray, claimed by U.S. Patent No. 5,482,934, and of Investigational New Drug ("IND") Application No. 65,488 for ciclesonide, claimed by U.S. Patent No. 5,482,934, which IND No. 65,488 was initially sponsored by Teijin America, Inc. (filed by Cato Research on behalf of Teijin America, Inc.) but which sponsorship has since been transferred such that IND No. 65,488 is now sponsored by ALTANA U.S.; that such NDA and IND contain a right of reference to IND No. 53,391 for ciclesonide currently sponsored by Sanofi-Aventis US Inc., a copy of the letter which provides this right of reference is attached as Exhibit B; that IND No. 53,391 was first filed by ALTANA, Inc. in Melville, NY, US agent for the listed IND sponsor, Byk Gulden Lomberg Chemische Fabrik GmbH in Konstanz Germany ("Byk Gulden") (which company since underwent a change in corporate form and transformation to Altana Pharma AG pursuant to section 190 ff UmwG (German Conversion Law) by virtue of a resolution dated May 27, 2002); that sponsorship of IND No. 53,391 was subsequently transferred to Aventis Pharmaceuticals, Inc., who subsequently transferred sponsorship to Sanofi-Aventis US

Inc.; that ALTANA PHARMA AG and ALTANA U.S. have the lawful right to refer to and rely on the information contained in IND No. 53,391; and that ALTANA PHARMA AG is entitled to rely on the marketing approval for OMNARIS™ (ciclesonide) Nasal Spray arising from NDA No. 22-004. Pursuant to the provisions of 37 C.F.R. § 1.740, your applicant hereby applies for an extension of the term of said United States patent of 1,748 days under 35 U.S.C. § 156, based on the materials set forth herein and in the accompanying papers. In the materials which follow herein, paragraph numbers correspond to the paragraph numbers in 37 C.F.R. § 1.740(a).

(1) The approved product is OMNARIS™ Nasal Spray, which is further identified as follows.

Chemical Name

(2'R)-2'-Cyclohexyl-11β-hydroxy-21-isobutyryloxy-16bH-dioxolo[5',4':16,17]pregna-1,4-diene-3,20-dione

also known as

pregna-1,4-diene-3,20-dione, 16,17-[[R-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α)-

also known as

(R)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexane carboxaldehyde, 21-isobutyrate

Generic Name

ciclesonide

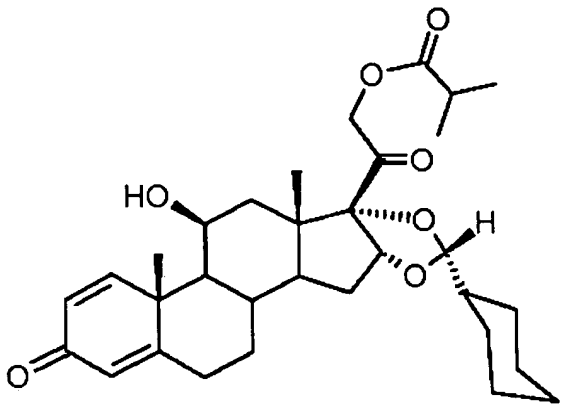
Molecular Formula

$C_{32}H_{44}O_7$

Molecular Weight

540.7

Chemical Formula



Note the approved package insert for OMNARIS™ Nasal Spray attached hereto as Exhibit C.

(2) OMNARIS™ Nasal Spray was subject to regulatory review under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355).

(3) OMNARIS™ Nasal Spray received permission for commercial marketing or use in the treatment of seasonal and perennial allergic rhinitis in patients 12 years of age and older under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) on October 20, 2006.

(4) The active ingredient in OMNARIS™ Nasal Spray is (2'R)-2'-Cyclohexyl-11β-hydroxy-21-isobutyryloxy-16bH-dioxolo[5',4':16,17]pregna-1,4-diene-3,20-dione

(ciclesonide). Said active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is December 19, 2006.

(6) The patent for which an extension is being sought is identified as follows.

Inventors: JOSE CALATAYUD, JOSE R. CONDE, and MANUEL LUNA

Patent No.: 5,482,934

Title: PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

Issued: January 9, 1996

Expires: January 9, 2013

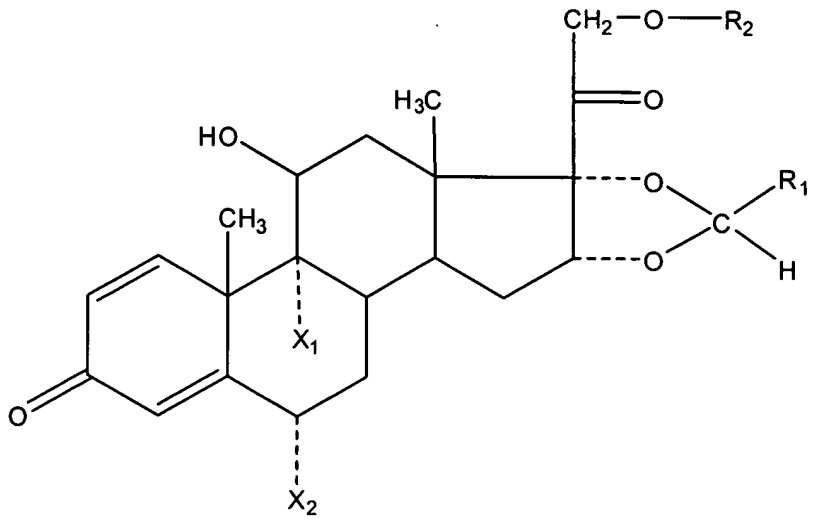
(7) A copy of United States Patent No. 5,482,934, the patent for which an extension is being sought, is attached hereto as Exhibit D.

(8) As is evident from the copy of United States Patent No. 5,482,934 attached hereto as Exhibit D, a certificate of correction has issued for United States Patent No. 5,482,934 correct the assignee name from Espacialidades Latinas Medicamentos Universales, S.A. to Elmuquimica Farmaceutica. Otherwise, no further certificates of correction and no disclaimers or reexamination certificates have issued for United States Patent No. 5,482,934. Copies of the receipts of maintenance fee payments are attached

hereto as Exhibit E.

(9) United States Patent No. 5,482,934 claims the approved product. Claims 1, 3, 8, 9, and 11, inclusive, claim the approved product per se. Claim 4 claims an anti-inflammatory drug which contains the approved product. Claim 6 claims a pharmaceutical composition which comprises the approved product. Claim 5 claims a method of treating inflammatory conditions by administering the approved product. Claim 7 claims a method for the treatment and control of inflammatory conditions by administering the approved product. The manner in which each applicable patent claim reads on the approved product is as follows.

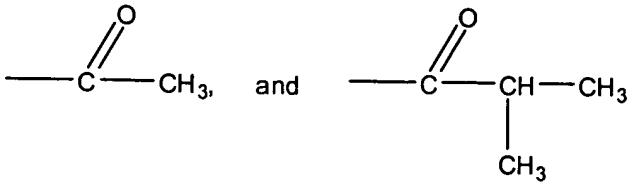
Claim 1 of U.S. 5,482,934 claims a chemical compound of the general formula:



in the form of an R epimer, an S epimer, or a stereoisomeric mixture of the R and S epimers in terms of the orientation of the substituents on the carbon atom at position 22, wherein:

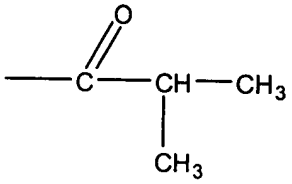
R_1 is cyclohexyl;

R_2 is a member selected from the group consisting of



and wherein X_1 and X_2 may be the same or different and each is a member selected from the group consisting of hydrogen and fluorine.

When R_1 is cyclohexyl, R_2 is



X_1 is hydrogen, X_2 is hydrogen, and the compound is in the form of an R epimer in terms of the orientation of the substituents on the carbon atom at position 22, the compound of the formula of claim 1 is ciclesonide. Therefore, claim 1 reads on the approved product.

Claim 3 of U.S. 5,482,934 claims the compounds of the formula of claim 1 in which the definitions of R_1, R_2, X_1, and X_2 are the same as in claim 1, but the epimeric form of the compound is restricted. In the restricted definition, the compound is in the form of the (22R)- epimer. Thus, claim 3 embraces ciclesonide and reads on the approved product.

Claim 4 of U.S. 5,482,934 claims an anti-inflammatory drug containing a compound of the formula of claim 1. Therefore, claim 4 embraces an anti-inflammatory drug containing ciclesonide and reads on the approved product.

Claim 5 of U.S. 5,482,934 claims a method of treating inflammatory conditions which comprises administering to a patient an anti-inflammatory effective amount of a compound of the formula of claim 1. Hence, claim 5 embraces the use of ciclesonide in

treating inflammatory conditions, and reads on an approved use of the product.

Claim 6 of U.S. 5,482,934 claims a pharmaceutical composition having anti-inflammatory properties which comprises as the active ingredient an effective amount of a compound of the formula of claim 1 together with a pharmaceutically acceptable carrier. Therefore, claim 6 embraces a pharmaceutical composition containing ciclesonide and reads on the approved product.

Claim 7 of U.S. 5,482,934 claims a method for the treatment and control of inflammatory conditions characterized by the topical administration to a patient of an effective dose of a compound of the formula of claim 1. Hence, claim 7 embraces the use of ciclesonide in treating and controlling inflammatory conditions, and reads on an approved use of the product.

Claim 8 of U.S. 5,482,934 claims the compounds of the formula of claim 1 which is [11β,16α(R,S)]-16,17-[cyclohexylmethylene)bis (oxy)]-11-hydroxy-21-(2-methyl- 1-oxopropoxy)pregna-1,4-diene-3,20-dione. Thus, claim 8 embraces ciclesonide and reads on the approved product.

Claim 9 of U.S. 5,482,934 claims a compound of claim 8 in which the epimeric form of the compound is restricted. In the restricted definition, the compound is in the form of the R- epimer. Thus, claim 9 embraces ciclesonide and reads on the approved product.

Claim 11 of U.S. 5,482,934 claims the compounds of the formula of claim 1 in which the definitions of R_1 and R_2, and the epimeric form of the compound, are the same as in claim 1, but the definitions of X_1, and X_2 are restricted. In the restricted definitions, each of X_1, and X_2 is hydrogen. Thus, claim 11 embraces ciclesonide and reads on the approved

product.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows.

(a) An exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act became effective for ciclesonide on January 21, 1998, i.e., the date the U.S. Food and Drug Administration (FDA) indicated there was no clinical hold and clinical trials could begin for Investigational New Drug ("IND") Application No. 53,391, initially filed on June 2, 1997 and resubmitted on December 15, 1997 by ALTANA, Inc in Mellville, NY, US agent for the listed IND sponsor, Byk Gulden (which company since underwent a change in corporate form and transformation to Altana Pharma AG), who subsequently transferred sponsorship to Aventis Pharmaceuticals, Inc., who subsequently transferred sponsorship to Sanofi-Aventis US Inc., and which IND No. 53,391 contains information regarding ciclesonide on which IND No. 65,488 and NDA No. 22-004 relied in seeking approval.

(b) A New Drug Application ("NDA") under section 505 of the Federal Food, Drug, and Cosmetic Act for OMNARIS™ Nasal Spray (ciclesonide) was initially submitted on December 21, 2005 by ALTANA U.S., as NDA No. 22-004 and was received by the FDA on December 22, 2005.

(c) NDA No. 22-004 was approved on October 20, 2006.

(11) A brief description of the significant activities undertaken by or for the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as Exhibit F.

(12) Applicant is of the opinion that United States Patent No. 5,482,934 is eligible for an extension under 35 U.S.C. § 156, and the length of the extension claimed is 1,748 days.

The requirements of 35 U.S.C. §§ 156(a) and (c)(4) have been satisfied as follows.

(a) U.S. Patent No. 5,482,934 claims a product, OMNARIS™ Nasal Spray (ciclesonide).

(b) U.S. Patent No. 5,482,934 is currently set to expire on January 9, 2013 (i.e., the term of the patent has not yet expired).

(c) The term of U.S. Patent No. 5,482,934 has never been extended.

(d) This application for extension is being submitted by ALTANA PHARMA AG, the owner of record of U.S. Patent No. 5,482,934, in accordance with the requirements of 35 U.S.C. § 156(d).

(e) The product, OMNARIS™ Nasal Spray (ciclesonide), has been subject to a regulatory review period under section 505 of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use, and permission for said commercial marketing or use is the first permitted commercial marketing or use under the Federal Food, Drug, and Cosmetic Act.

(f) No patent has to this date been extended, nor has any other extension been applied for, for the regulatory review period which forms the basis for this application for extension of the term of U.S. Patent No. 5,482,934.

The length of extension of the term of U.S. Patent No. 5,482,934 of 1,748 days claimed by applicant was determined according to the provisions of 37 C.F.R. § 1.775 as follows.

(a) According to 37 C.F.R. § 1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate according to paragraphs (d)(1) through (d)(6) of 37 C.F.R. § 1.775.

(b) According to 37 C.F.R. § 1.775(c), the regulatory review period is the sum of (A) the number of days in the period beginning on the date on which the exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act became effective and ending on the date the NDA was initially submitted under section 505 and (B) the number of days in the period beginning on the date the NDA was initially submitted and ending on the date the NDA was approved. The exemption under subsection 505(i) became effective on January 21, 1998 (for IND No. 53,391), the filing of the NDA for ciclesonide nasal spray (NDA No. 22-004) was initially received by the FDA on December 22, 2005 and the NDA was approved on October 20, 2006. Hence the regulatory review period is the sum of the periods from January 21, 1998 to December 22, 2005 and from December 22, 2005 to October 20, 2006. This is the sum of 2,892 days and 302 days, which is 3,194 days.

(c) According to 37 C.F.R. § 1.775(d)(1)(i), the number of days in the regulatory review period which were on or before the date on which the patent issued must be subtracted. Since U.S. Patent No. 5,482,934 issued on January 9, 1996 and the regulatory review period began afterwards on January 21, 1998 (i.e., the date on which the exemption under subsection 505(i) became effective), this section does not apply, and the regulatory review period

remains as 3,194 days.

(d) 37 C.F.R. § 1.775(d)(1)(ii) does not apply.

(e) According to 37 C.F.R. § 1.775(d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R. § 1.775(c)(1). This is one half of 2,892 days, which is 1,446 days. After subtraction, and ignoring half days in the subtraction, this now leaves a reduced regulatory review period of 1,748 days.

(f) When the reduced regulatory review period of 1,748 days is added to the expiration date of U.S. Patent No. 5,482,934 (January 9, 2013), this gives a date of October 23, 2017. This latter date is earlier than October 20, 2020, the date obtained by adding 14 years to the date of approval of the approved product. Under paragraphs (d)(2) to (d)(4) of 37 C.F.R. § 1.775, applicant is entitled to an extension of patent term until a date that is no later than October 23, 2017, the earlier of the two dates of extension of patent term.

(g) The five-year limitation of 35 U.S.C. § 156(g)(6)(A) and 37 C.F.R. § 1.775(d)(5) applies to this application, because U.S. Patent No. 5,482,934 issued after the date of enactment of 35 U.S.C. § 156. When 5 years is added to the expiration date of U.S. Patent No. 5,482,934 (January 9, 2013), this gives a date of January 9, 2018. The date obtained by adding the extension sought (1,748 days) to the expiration date of U.S. Patent No. 5,482,934 is October 23, 2017, which is earlier than January 9, 2018. Hence, applicant is in compliance with 35 U.S.C. § 156(g)(6)(A) and 37

C.F.R. § 1.775(d)(5).

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the 1,748 day extension being sought to the term of United States Patent No. 5,482,934.

(14) The prescribed fee for receiving and acting on this application for extension is attached herewith. Any required fee deficiency is specifically and expressly authorized to be charged to Deposit Account No. 14-0112 in connection with this matter.

(15) Please address all inquiries and correspondence relating to this application for patent term extension to:

Gary M. Nath
Nath and Associates
112 S. West Street
Alexandria, VA 22314
Tel.: (703) 548-6284
Fax: (703) 683-8396

Two duplicates of these application papers, for a total of three copies, certified as such, are enclosed herewith.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Date: December 15, 2006
NATH & ASSOCIATES PLLC
112 S. West Street
Alexandria, VA 22314
Tel: (703) 548-6284
Fax: (703) 683-8396
GMN:JBG:\patentextension.doc

Gary M. Nath
Reg. No. 26,965
Joshua B. Goldberg
Reg. No. 44,126
Customer No. 34375

EXHIBIT A

PATENTS ONLY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	:	Roeb & Co. S.L.
FOR	:	ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A. (ELMU, S.A.)
SERIAL NO.	:	578,942
FILED	:	September 7, 1990
EXAMINER	:	
ART UNIT	:	
LAST OFFICE ACTION	:	
ATTORNEY DOCKET NO.	:	RCS 2 001

Cleveland, Ohio 44114-2518
August 5, 1991

ASSIGNMENT TRANSMITTAL LETTER

Commissioner of Patents
and Trademarks
Washington, DC 20231

Dear Sir:

Please record the attached original document or copy thereof.

1. Name of Party(ies) conveying an interest:

Jose Calatayud, Jose Ramon Conde and Manuel Luna

P 30002 08/08/91 07578942 06-0308 030 518 8.00CH

2. Name and Address of Party(ies) receiving an interest:

Name: ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A. (ELMU, S.A.)

Street Address: Edifico Elmu, Carretera Nacional III, KM 23, 28500 ARGANDA DEL REY

City: Madrid

State: SPAIN ZIP:

91585489

3. Description of the interest conveyed:

_X_ Assignment ____ Change of Name

____ Security Agreement ____ Merger

Other _____

4. Application number(s) or patent number(s).

The execution date of the application is:

September 7, 1990
Date

A. Patent Application No.(s)	B. Patent No.(s)
578,942	

Additional sheet attached? ____ Yes _X_ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Richard J. Minnich
(type name of attorney)

Firm: Fay, Sharpe, Beall, Fagan, Minnich & McKee

Address: 1100 Superior Avenue, Suite 700

City: Cleveland

State: Ohio ZIP: 44114-2518

6. Number of applications and patents involved: 1

7. Amount of fee enclosed or authorized to be charged:

$8.00

8. Deposit Account Number (attached duplicate copy of this form if paying by Deposit Account): 06-0308

DO NOT USE THIS SPACE

9. Date of execution of attached document:

July 31, 1991

Respectfully submitted,

FAY, SHARPE, BEALL,
FAGAN, MINNICH & MCKEE

Richard J. Minnich
Reg. No. 24,175
1100 Superior Avenue
Suite 700
Cleveland, OH 44114-2518
(216) 861-5582

ASSIGNMENT

WHEREAS we, **Jose Calatayud** of Emilio Vargas, 2, Madrid, Spain; **Jose Ramon Conde** of Emilio Vargas, 2, Madrid, Spain; and, **Manuel Luna** of Emilio Vargas, 2, Madrid, Spain, having invented certain new and useful improvements in

NEW PREGNA-1, 4-DIENE-3, 20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

said application having been filed on the 7th day of September, 1990, do hereby, in consideration of One Dollar ($1.00) and other good and valuable consideration, receipt of which is hereby acknowledged, sell, assign, and transfer unto

ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A. (ELMU,S.A.)

having a principal place of business at:

Edificio Elmu
Carretera Nacional III, Km.23
28500 ARGANDA DEL REY (Madrid)
SPAIN

the full and exclusive right, title and interest in and to the said invention in the United States and its territorial possessions, and in all foreign countries with all rights under the International Convention including the right to claim priority, and the entire and exclusive right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries, and in and to any and all divisions, reissues, and continuations, and extensions thereof.

We, therefore, authorize and request the Patent Office officials in the United States and in any and all foreign countries to issue any and all Letters Patent, when granted, solely to the said:

ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A. (ELMU, S.A.) for its sole use, its successors, and assigns.

Signed at Madrid, this 31 day of July, 1991.

Jose Calatayud

WITNESS:

Signed at Madrid this 31 day of July, 1991.

Jose Ramon Conde

WITNESS:

Signed at Madrid, this 31 day of July, 1991.

Manuel Luna

WITNESS:

RECORDED
PATENT AND TRADEMARK
OFFICE
AUG -6 1991

REEL 5791 FRAME 574

(Assignment (Document) Cover Sheet [16-6] —page 1 of 8)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: *"Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C. 20231, unless they are filed together with new applications or with a petition under § 3.81(b)." 37 CFR 3.27*

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: *"A cover sheet may not refer to both patents and trademarks." 37 CFR 3.31(b).*

Attached please find an assignment (document) for recordal.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this "Assignment (Document) Cover Sheet (along with any paper referred to as being attached or enclosed) is being deposited on the date shown below with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(check and complete appropriate item below):

☐ 37 CFR 1.8(a) with sufficient postage as first class mail

or

☐ 37 CFR 1.10 as "Express Mail Post Office to Addressee" Mailing Label No._____

Michelle M. Velotta
(Type or print name of person mailing paper)

Date May 12, 1993

Michelle M Velotta
(Signature of person mailing paper)

3355

5950

91668313

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 CFR 3.21 and 37 CFR 3.31(a)(4))

NOTE: *"An assignment relating to a patent must identify the patent by the patent number. An assignment relating to a national patent application must identify the national patent application by the application number (consisting of the series code and the serial number, e.g., 07/123,456) or the serial number and the filing date. An assignment relating to an international patent application which designates the United States of America must identify the international application by the international application number (e.g., PCT/US90/01234)." 37 CFR 3.21.*

1. This assignment is for the following patent application and/or issued patent:

National application: SN: 07 /578,942 filed on September 7, 1990
International application: PCT/ /
Patent No: Issued: ***

(complete if applicable) which was previously assigned August 6, 1991

Reel 5791
Frame 570

(also complete the following, if applicable)

☐ and also for the applications and/or patents shown on the attached list of FURTHER APPLICATION(S) and/or PATENT(S) BEING ASSIGNED

Number of pages added 0

***Inventors: Calatayud, Jose
Conde, Jose Ramon
Luna, Manuel

Title: New Pregna-1, 4-Diene-3, 20-Dione-16-17-Acetal-21 esters Process for Their Preparation, Composition, and Methods for the Treatment of Inflammatory Conditions

(Assignment (Document) Cover Sheet [16-6] —page 3 of 8)

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE (37 CFR 3.28(a)(6))

(6) 2. A. The total number of applications and/or patents identified in this cover sheet is 1.

(7) B. The total fee is (37 CFR 1.21(h)):

1 x $40.00 = $40.00

Total number of applications and/or patents

(Fee paid with original submission of Assignment)

C. Payment of fee is made by:

☐ attached check for $_____

☐ please charge Account _____

the sum of $_____

A duplicate of this cover sheet is attached

(8) Please charge Account 06-0308 for any fee deficiency or credit to account any overpayment.

NAME OF PARTY(IES) CONVEYING INTEREST (37 CFR 3.31(a)(1))

(1) 3. The party(ies) conveying interest is (are):

Name 1: Especialidades Latinas Medicamentos Universales, S.A.

Name 2:

Name 3:

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST (37 CFR 3.31(a)(2))

(2) 4. The rights are being conveyed to:

Name: EUROFIN, S.A.

Address: Luxembourg, 8, rue Zithe

Grand Duchy of Luxembourg

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 CFR 3.31(a)(3))

03 5. The accompanying document intends to accomplish:

- ☒ an assignment 01
- ☐ a securily agreement
- ☐ a merger
- ☐ a license
- ☐ a change of name
- ☐ a change of address
- ☐ other

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 CFR 3.31(a)(5))

(5) 6. Please address correspondence to:

Name: Richard J. Minnich
Address: 1100 Superior Avenue, Suite 700
Cleveland, Ohio 44114-2518
Telephone No.: (216) 861-5582

Fay, Sharpe, Beall, Fagan, Minnich & McKee

6522 0569

(Assignment (Document) Cover Sheet [16-6] —page 5 of 8)

DATE ASSIGNMENT (DOCUMENT) EXECUTED (37 CFR 3.31(a)(7))

(3) 7. The attached assignment (document) was executed on December 3, 1992.
(date)

LANGUAGE OF ASSIGNMENT (DOCUMENT) TO BE RECORDED

NOTE: "The Office will accept and record non-English language documents only if accompanied by a verified English translation signed by the individual making the translation." 37 CFR 3.26.

8. The attached document:

☒ is in the English language
☐ is not in the English language and a verified English translation signed by the individual making the translation is attached.

ORIGINAL DOCUMENT OR TRUE COPY SUBMITTED

NOTE: "Either the original document or a true copy of the original document may be submitted for recording. Only one side of each page shall be used. The paper used should be flexible, strong, white, non-shiny, durable, and preferably no larger than 21.6 x 33.1 cm. (8 1/2 x 14 inches) with a 2.5 cm. (one-inch) margin on all sides." 37 CFR 3.24.

9. Submitted herewith is:

☐ the original document
☒ a true copy of the original document

6950 12/95

(Assignment (Document) Cover Sheet [16-6] —page 7 of 8)

STATEMENT (37 CFR 3.31(a)(9)) AND SIGNATURE 37 CFR 3.31(a)(10))

(9) 13. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Date: 5-12-93

(10) Pgs. 28

(Name of party submitting document)

(Signature of party submitting document)

SIGNATURE OF ATTORNEY

Reg. No. 24,175

Tel. No. (216) 861-5582

Richard J. Minnich

Type or print name of Attorney

1100 Superior Avenue, Suite 700

P.O. Address

Cleveland, Ohio 44114-2518

Fay, Sharpe, Beall, Fagan, Minnich & McKee

6522 0570

40.00 581 D

(Assignment (Document) Cover Sheet [16-6] —page 1 of 8)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C. 20231 unless they are filed together with new applications or with a petition under § 3.81(b). 37 CFR 3.27.

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: A cover sheet may not refer to both patents and trademarks. 37 CFR 3.31(b).

Attached please find an assignment (document) for recordal.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this "Assignment (Document) Cover Sheet (along with any paper referred to as being attached or enclosed) is being deposited on the date shown below with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(check and complete appropriate item below)

XX 37 CFR 1.8(a) with sufficient postage as first class mail

or

☐ 37 CFR 1.10 as "Express Mail Post Office to Addressee" Mailing Label No.

Michelle M. Velotta
(Type or print name of person mailing paper)

Date March 15, 1993

Michelle M. Velotta
(Signature of person mailing paper)

160 MG 04/02/93 07578942 1 581 40.00 CK

91668313

ETUDE

DE

Me JOSEPH KERSCHEN

NOTAIRE

A

LUXEMBOURG-EICH

Dépositaire des Minutes
des notaires Roger Wurth, Ernest Brincour et Jules Gruber

No 37.377 du 3 décembre 1992

VENTE DE BREVET

Whereof the present notarial deed was drawn up in Luxembourg, on the day named at the beginning of this document.

The document having been read to the persons appearing, known to the undersigned notary by their surnames, names, civil status and residences, the said persons appearing signed together with the notary the present original deed.

SUIT LA TRADUCTION FRANCAISE DU TEXTE QUI PRECEDE

L'an mil neuf cent quatre-vingt-douze, le trois décembre.

Pardevant Maître Joseph Kerschen, notaire de résidence à Luxembourg-Eich.

Ont comparu:

1) Especialidades Latinas Medicamentos Universales, S.A. (Elmu, S.A.), une société de droit espagnol ayant son siège social à Madrid, Crtra. de Valencia, Km. 23, Arganda del Rey,

ci-après dénommée "le Vendeur",

représentée aux fins des présentes par M. Tom Loesch, Avocat, demeurant à Luxembourg, aux termes d'une procuration par acte notarié passé à Madrid en date du 22 juin 1992, qui restera annexée aux présentes pour être enregistrée avec elles.

2) Eurofin S.A., société de droit luxembourgeois ayant son siège social à Luxembourg, 8, rue Zithe,

ci-après dénommée "l'Acquéreur",

représentée aux fins des présentes par M. René Diederich, administrateur et M. Tom Loesch, administrateur.

Lesquels comparants, agissant

particulièrement adapté au traitement de l'asthme des bronches, ci-après appelé "le Produit".

2) Le Vendeur a déposé des demandes de brevet du Produit auprès des services compétents respectifs des pays suivants:

- FRANCE : Demande n° 91 10682
- [illegible] : Demande n° [illegible]
- [illegible] : Demande n° [illegible]
- [illegible] : Demande n° [illegible]
- GRECE : Demande n° [illegible]
- [illegible] : Demande n° [illegible]
- EPO : Demande n° 9202872
- BELGIQUE : Demande n° 9200816
- LUXEMBOURG : Demande n° 88001
- JAPON : Demande n° 227418
- AUSTRALIE : Demande n° 8368691
- SUISSE : Demande n° 02619-913
- R.O.C. : Demande n° 15617/91
- CANADA : Demande n° 2.050.812-4
- AUTRICHE : Demande n° A1769/91
- U.S.A. : Demande n° 578942

3) Le Produit est une invention du Vendeur, il n'est pas compris dans l'état de la technique, il a uniquement été divulgué dans des publications et lors d'événements à caractère scientifique et à des membres de l'industrie pharmaceutique.

4) Le Produit fait toujours l'objet de recherches par le Vendeur, lesdites recherches étant réalisées avec l'aide financière des services administratifs espagnols compétents.

5) Les prévisions quant au développement du Produit ont été établies en quatre étapes comme suit:

Première étape : Essais - sécurité et première pharmacologie clinique.

Deuxième étape : Essais - efficacité clinique et continuation de la pharmacologie clinique.

Troisième étape : Essais - développements cliniques tardifs.

Quatrième étape : Enregistrement du Produit pour la vente.

6) Le Produit n'a pas encore atteint sa première étape de développement, étant

et adapté à l'usage à l'homme une fois qu'il aura atteint la quatrième étape.

En vertu de ce qui a été énoncé ci-dessus, les parties concluent le présent contrat conformément aux dispositions suivantes:

Article 1. DEFINITIONS

Le Produit visé par ce contrat d'achat et de vente et qui n'a pas présentement de nom commercial, renferme le CICLESONIDE comme composant actif; ce contrat autorisera la fabrication, la distribution et la commercialisation du Produit dans le Territoire Contractuel énuméré à l'Article 3 ci-dessous.

Article 2. OBJETS DU CONTRAT

Par ce contrat, le Vendeur cède à l'Acquéreur, et ce dernier acquiert, le brevet du Produit ainsi que tous les droits de fabrication, distribution et commercialisation du Produit tels que définis à l'Article 1.

La vente du brevet du Produit comprend:

a) La cession à l'Acquéreur de tous les droits et obligations ayant trait à la fabrication, la distribution et la commercialisation du Produit que possède le Vendeur.

b) La cession à l'Acquéreur de toutes les demandes de brevet énumérées ci-dessus sub 2) dans le préambule, ainsi que le droit pour l'Acquéreur de déposer en son nom propre toutes demandes de brevet du Produit auprès des services compétents de tous les pays compris dans le Territoire Contractuel défini à l'Article 3 de ce contrat qui ne sont pas inclus dans la liste de ceux énumérés sub 2) dans le préambule.

c) Toutes informations et tous documents liés au brevet et au Produit, indépendamment du lieu où ils ont été publiés.

d) Le droit de l'Acquéreur de mener autant d'activités et d'exécuter autant de démarches qui lui semblent nécessaires de façon à faire les tests, les expériences et/ou les essais permettant d'atteindre le développement final du Produit, de telle façon que le Produit soit finalement adapté à l'usage à l'homme. A

cette fin, l'Acquéreur pourra s'associer avec toutes sociétés ou tous laboratoires ou demander un avis d'ordre technique et/ou une assistance à tous ceux qu'elle estime nécessaire. Les résultats desdits tests, expériences et/ou essais, s'il y en a, seront immédiatement adressés au Vendeur, qui les utilisera de façon à atteindre aussitôt que possible une étape plus avancée du développement du Produit, tel qu'énoncé sub 5) et 6) du Préambule au présent contrat, c'est-à-dire, les résultats des tests, expériences et/ou essais accomplis par l'Acquéreur, soit lui-même ou dans le cadre d'une association, retourneront entièrement au Vendeur, exclusivement en Espagne et dans le seul but d'accélérer l'accession à la quatrième étape de développement du Produit.

Les résultats des expériences, test et/ou essais, tels qu'énoncés dans le présent article, peuvent être utilisés par l'Acquéreur, dans le cadre du territoire énoncé à l'Article 3, pour obtenir l'inscription du Produit au Registre de la Santé ou pour tout autre but qu'il pourrait estimer approprié ou nécessaire.

Les dépenses encourrues par l'Acquéreur s'il s'associe ou lors de l'exécution des test, expériences et/ou essais seront à sa propre charge.

Article 3. TERRITOIRE

L'Acquéreur aura le droit exclusif de disposer librement du brevet et du Produit et de mener les expériences, tests et/ou essais du Produit, tel qu'énoncé à l'Article précédent, dans tous les pays du monde à l'exclusion de l'Espagne (ci-après dénommés "le Territoire Contractuel"). Dans le cadre du Territoire Contractuel, l'Acquéreur pourra céder, vendre ou disposer du brevet et du Produit sans aucunes limitations, accorder autant de licences qu'il juge approprié ou nécessaire, s'associer pour le développement du Produit, et introduire en son nom propre auprès des services compétents des pays compris dans le Territoire Contractuel autant de demandes de brevet qu'il estimera nécessaire ou approprié. De son côté, le Vendeur ne sera pas autorisé à utiliser le Produit dans le Territoire Contractuel ou d'accorder des licences pour sa fabrication.

L'Acquéreur recevra la propriété du brevet du Produit pour la fabrication, la distribution et la commercialisation du Produit, de manière directe ou indirecte, pour l'ensemble du Territoire Contractuel.

Par conséquent, l'Acquéreur n'aura aucun droit sur le brevet du Produit en Espagne où le Vendeur conserve la pleine propriété du brevet du Produit, du droit exclusif de son procédé de fabrication, des résultats des expériences, test et/ou essais menés par l'Acquéreur dans le cadre du Territoire Contractuel, ainsi que tous les autres droits de propriété industrielle, y compris les expériences et essais, les documents y relatifs, le savoir-faire et les formules secrètes de fabrication, de distribution et de vente du Produit, conformément à ce qui est stipulé à l'Article 9.

Article 4. DEMANDES DE BREVET

Le Vendeur accepte de déposer, si nécessaire, auprès des services compétents des pays énumérés sub 2) dans le préambule les demandes correspondantes de telle sorte que les brevets demandés soient accordés à l'Acquéreur et non au Vendeur. Tous les frais liés aux demandes de brevet lors de l'enregistrement des brevets au nom de l'Acquéreur seront à la charge de ce dernier.

Article 5. QUANTITE ET CONNAISSANCE DU PRODUIT

L'Acquéreur déclare qu'il connait et est familiarisé avec l'état de développement actuel du Produit, ainsi que ses effets et applications.

Par conséquent, et en raison de cette connaissance, l'Acquéreur n'introduira aucune réclamation quelconque à l'encontre du Vendeur à raison du procédé de fabrication ou tout aspect dérivé du Produit ou de ses résultats définitifs.

A la demande de l'Acquéreur, le Vendeur assume la responsabilité d'assurer un contrôle technique du procédé de fabrication du Produit et garantit que le Produit est adapté aux buts pour lesquels il a été inventé, étant entendu que l'Acquéreur et ses licenciés feront adéquatement usage de son procédé de fabrication.

Le Vendeur ne sera pas tenu responsable des éventuelles modifications du procédé de fabrication du Produit introduite par l'Acquéreur ou par les personnes ou personnes morales auxquelles l'Acquéreur accorde des licences, ou pour les effets secondaires nuisibles que de telles modifications pourraient éventuellement causer.

Article 6. PRIX

Le prix de vente du brevet du Produit et de ses droits est fixé comme suit:

a) VINGT-CINQ MILLION DE PESETAS (25.000.000 Ptas.) une fois que le Produit a atteint de façon satisfaisante la première étape de son développement, telle qu'énoncée sub 5) du Préambule du présent contrat.

b) VINGT-CINQ MILLION DE PESETAS (25.000.000 Ptas.) une fois que le Produit a atteint de façon satisfaisante la deuxième étape de son développement, telle qu'énoncée sub 5) du Préambule du présent contrat.

c) TRENTE-CINQ MILLION DE PESETAS (35.000.000 Ptas.) une fois que le Produit a atteint de façon satisfaisante la troisième étape de son développement, telle qu'énoncée sub 5) du Préambule du présent contrat.

d) QUINZE MILLION DE PESETAS (15.000.000 Ptas.) lors de l'inscription du Produit au Registre de la Santé dans le Territoire Contractuel.

Les parties contractantes déclarent expressément que la valeur du brevet du Produit et des droits découlant de celui-ci qui sont l'objet de ce contrat correspondent parfaitement et objectivement au prix convenu, et elles renoncent expressément à toute action et/ou défense qui aurait pour effet d'annuler les effets juridiques de ce contrat.

Article 7. DEFAUT DE PAIEMENT

Il est expressément convenu que si l'Acquéreur ne respecte pas ce contrat et, en particulier, que si l'Acquéreur manque de payer le prix convenu et/ou les redevances convenues au moment prévu, le Vendeur aura le

droit d'exiger par lettre recommandée; à sa convenance, l'exécution du contrat ou son annulation, assorties dans chacun des cas de dommages-intérêts. En cas d'annulation du contrat, la propriété ainsi que le droit d'usage et les autres droits liés à la propriété du brevet du Produit, qui sont l'objet de ce contrat, seront entièrement restitués au Vendeur. Dans ce cas, l'Acquéreur n'aura pas le droit de réclamer au Vendeur une compensation quelconque et/ou le remboursement de tous montants ou redevances reçus.

Article 8. PRIVILEGES

Le Vendeur déclare expressément que les demandes de brevets énumérées sub 2) dans le Préambule du présent contrat sont libres de tous privilèges, hypothèques, saisies et, de manière générale, de toutes mesures judiciaires ou extra-judiciaires qui puissent limiter les droits de propriété et de libre disposition du brevet du Produit d'une manière quelconque.

Article 9. OBLIGATION DE PRODUIRE

L'Acquéreur accepte de produire, distribuer et vendre le Produit dans le Territoire Contractuel endéans les deux ans qui suivent la date à laquelle débute la production du Produit en Espagne, à moins qu'il n'en soit empêché par la législation d'un des pays inclus dans le Territoire Contractuel.

L'Acquéreur autorisera la vente du Produit par le Vendeur dans les pays appartenant au Territoire Contractuel où l'Acquéreur n'a pas commencé à commercialiser le Produit dans le délai mentionné ci-dessus.

Article 10. AMELIORATIONS

Les parties conviennent de s'informer mutuellement de toutes les améliorations introduites dans le procédé de fabrication du Produit. L'Acquéreur accepte d'imposer une telle obligation à tous les tiers auxquels il pourra éventuellement accorder une licence d'exploitation du brevet du Produit ou d'exploitation des brevets accordés de telle façon à ce que tous les tiers informent le Vendeur de telles améliorations. De plus, l'Acquéreur accepte d'imposer à ces tiers l'obligation d'envoyer au Vendeur des copies de tous livrets, brochures, informations

médicales et de toutes autres explications que ces tiers peuvent donner ou imprimer à propos du Produit et/ou des brevets déjà accordés.

Les améliorations seront considérées comme étant la propriété de la partie les ayant faites, la partie en question devra cependant offrir à l'Acquéreur, sans frais à charge de ce dernier, toutes informations sur ces améliorations. L'Acquéreur devra inclure dans ses contrats de licence conclus avec des tiers l'obligation pour ces derniers de fournir au Vendeur toutes informations et documents disponibles sur la(les) amélioration(s) apportée(s) au Produit comme il est précisé à l'alinéa précédent..

La partie ayant fait l'amélioration, quelle qu'elle soit, accordera gratuitement à l'Acquéreur et au Vendeur, si il est un tiers, ou quelque soit le cas, s'il s'agit de l'un d'entre eux, une licence d'exploitation des procédés et des améliorations brevetables pour une période de 10 ans.

Article 11. SECRET

L'Acquéreur accepte de garder secret le contenu du brevet du Produit qui est l'objet de ce contrat et des documents et informations relatifs à celui-ci fournis par le Vendeur. L'Acquéreur devra également prendre les mesures appropriées pour limiter l'accès aux composants du Produit au plus petit nombre possible de collaborateurs.

Au cas où l'Acquéreur accorde une licence ou dispose de toute autre manière du brevet du Produit, des documents ou des informations en faveur d'un tiers, l'Acquéreur accepte d'imposer une obligation de discrétion à ces tiers de la manière prévue ici et, de plus, l'Acquéreur accepte d'informer le Vendeur de ces cessions.

Article 12. CONDITIONS DIVERSES

L'annulation d'une disposition de ce contrat n'entachera pas de nullité les dispositions restantes aussi longtemps que ce contrat n'est pas dénaturé ou affecté en ses termes essentiels.

Toute modification ou addition au contrat sera faite par écrit. Seules les communications faites par écrit et envoyées

aux adresses mentionnées à l'Article 14 du contrat seront reconnues comme étant valables dans le cadre de l'exécution du contrat.

Article 11. REGISTRE

Le Vendeur accepte de fournir tous les moyens nécessaires à l'Acquéreur afin que la propriété du brevet du Produit soit enregistrée au nom de l'Acquéreur auprès des services compétents du Territoire Contractuel. De son côté, l'Acquéreur s'engage, tel que cela est énoncé à l'Article 2, à immédiatement informer le Vendeur des résultats de tous tests, expériences et/ou essais menés sur le Territoire Contractuel. Toutes dépenses liées avec les demandes de brevets en faveur de l'Acquéreur sur le Territoire Contractuel et selon le cas, celles liées à la restitution de la propriété du brevet au Vendeur en cas d'expiration ou d'annulation du contrat incombera à l'Acquéreur, sera à charge de ce dernier.

Article 12. LANGUE, ADRESSE, COMPETENCE ET ARBITRAGE

Pour les besoins des communications qui devront être ou pourront être faites en relation avec ce contrat, les adresses des parties sont :

Le Vendeur : [illegible] de Velázquez, no. 24, Arganda del Rey, Madrid, Espagne.

L'Acquéreur : [illegible], rue [illegible], Luxembourg, Grand-Duché de Luxembourg.

Ce contrat est soumis et sera interprété conformément aux lois du Grand-Duché de Luxembourg.

Tout litige entre les parties touchant à l'interprétation ou à l'exécution de ce contrat qui ne pourra être réglé à l'amiable sera soumis, dans [illegible] Ordinaires ou Commerciales de la Chambre Internationale de [illegible] Paris, conformément aux règles de procédure de ladite Chambre, dont l'arbitrage sera sans recours et liera les parties.

Article 13. CESSION A DES TIERS

EUROFIN a le droit de vendre le brevet du Produit et ses droits de fabrication, de distribution et de commercialisation du

Produit ou de céder à des tiers les droits et obligations découlant de ce contrat endéans le Territoire Contractuel.

FRAIS

Les frais, dépenses, charges et rémunération sous quelque forme que ce soit, qui incombent à l'Acquéreur en raison des présentes, s'élèvent approximativement à 100.000.-LUF .

Le notaire instrumentant, qui comprend l'anglais déclare par les présentes que sur demande des comparants, le présent acte notarié est rédigé en anglais suivi d'une version française; sur demande des mêmes comparants et en cas de divergences entre le texte anglais et le texte français, le texte anglais fera foi.

Dont acte.

Fait et passé à Luxembourg.

Date qu'en tête des présentes.

Et après lecture faite et interprétation donnée aux comparants, connus du notaire par leurs noms, prénoms usuels, état et demeure, ils ont signé avec Nous, notaire le présent acte.

signé: Me Tom LOESCH, Me rené DIEDERICH, Me Joseph KERSCHEN

Enregistré à Luxembourg A.C. le 7 décembre 1992

Volume 862A, folio 66, case 2

Reçu: cent francs

Le Receveur (signé) HERTGES

Coût

T: 400.-

R:1000.-

POUR EXPEDITION CONFORME

délivrée aux parties sur demande

Luxembourg-Eich, le 11 décembre 1992

REEL FRAME 0582 6522

Dixième et dernier feuillet

BP 0104568

Yo, JOSE M. RODRIGUEZ-ESCUDERO, Notario de esta Capital y Colegio.

DOY FE: De que la presente fotocopia, extendida en 11 folios de papel común cada uno de los cuales numera y sella, reproduce exactamente el documento fotocopiado; dejando nota del mismo en el Libro Indicador con el n.º

Madrid, a 3 FEB. 1993

REEL FRAME 6522 0583

Apostille (o legalización única)
(Convention de La Haye du 5 octobre 1961)
(Real Decreto 2433/1978, de 2 de octubre)

1. País: *España*
   El presente documento público
2. Ha sido firmado por D. José Manuel Rodríguez-Escudero Sánchez
3. Actuando en calidad de *NOTARIO*
4. Se halla sellado/timbrado con *el de su Notaría*

CERTIFICADO

5. En Madrid 6. El 4 Febrero 1993
7. Por el Decano del Colegio Notarial de Madrid
8. Con el número SS 158
9. Sello/timbre: 10. Firma:

D. José María Lucena Conde
Miembro de la Junta Directiva en funciones de Decano

In the year one thousand nine hundred and ninety-two, on the 3rd of December.

Before us, Maître Joseph Kerschen, Notary, with residence at Luxembourg-Eich.

There appeared :

1) Especialidades Latinas Medicamentos Universales, S.A. (Elmu, S.A.), a company organised and existing under the laws of Spain with its registered office in Madrid, Crtra. de Valencia, Km. 23, Arganda del Rey,

hereinafter THE SELLER

hereby represented by Mr Tom Loesch, Attorney at Law, residing in Luxembourg,

by virtue of a proxy given at Madrid on 22nd June, 1992, which shall be annexed to the present deed for the purpose of registration.

2) Eurofin S.A., a company organised and existing under the laws of Luxembourg with its registered office in Luxembourg, 8, rue Zithe,

hereinafter THE BUYER

hereby represented by Mr René Diederich, Director, and Mr Tom Loesch, Director.

The said persons appearing, acting in their above-mentioned capacities, have requested the undersigned notary to record the following Sale and Purchase Agreement which they declare to enter into between themselves :

CONSIDERING

1) That the SELLER is developing a new pharmaceutical product whose chemical structure is CICLESONIDE, derived from a steroid especially suitable for bronchial asthma treatment, hereinafter THE PRODUCT.

2) That THE SELLER has deposited the patent applications of THE PRODUCT with the corresponding competent departments of the following countries:

- FRANCE : Application n° 91 10682
- ITALY : Application n° 91A002296

- UNITED KINGDOM : Application n° 9118967.0.
- GERMANY : Application n° P41295358
- GREECE : Application n° 910100353
- PORTUGAL : Application n° 98897
- NETHERLANDS : Application n° 9101472
- BELGIUM : Application n° 9100816
- LUXEMBOURG : Application n° 88001
- JAPAN : Application n° 227418
- AUSTRALIA : Application n° 8368691
- SWITZERLAND : Application n° 02619-913
- R.O.C. : Application n° 15617/91
- CANADA : Application n° 2.050.812-4
- AUSTRIA : Application n° A1769/91
- U.S.A. : Application n° 578942

3) That THE PRODUCT is an invention of THE SELLER, that it is not included in state-of-the-art technology, that it has only been made accessible to publications and scientific events and to certain entities in the pharmaceutical industry.

4) That THE PRODUCT is still subject to scientific research by THE SELLER, said research being carried out with the financial support of the competent Spanish administrative departments.

5) That the development forecast of THE PRODUCT has been established in four stages as follows:

Stage 1: Trials - safety and early clinical pharmacology.

State 2: Trials - clinical efficacy and further clinical pharmacology.

Stage 3: Trials - later clinical developments.

Stage 4: Registration of PRODUCT for sale.

6) THE PRODUCT has not already reached its first stage of development, being expressly understood that THE PRODUCT will be ready and fit for human application purposes once it has reached the fourth stage.

That by virtue of what has been stated herein, the parties enter into the present agreement according to the following:

Article 1. DEFINITIONS

THE PRODUCT covered by this buying and selling agreement, which does not yet have a

commercial name, has CICLESONIDE as an active ingredient, and will allow its manufactoring, distribution and commercialization in THE CONTRACTUAL TERRITORY detailed in Article 3 below.

Article 2. PURPOSES OF THE AGREEMENT

By means of this agreement, THE SELLER transfers to THE BUYER and the latter acquires the patent of THE PRODUCT as well as all the rights to manufacture, distribute and commercialize THE PRODUCT as defined in Article 1.

The sale of the patent of THE PRODUCT includes:

a) The transfer to THE BUYER of all the rights and obligations that THE SELLER has for the manufacture, distribution and commercialization of THE PRODUCT.

b) The transfer to THE BUYER of all the patent applications listed in Recital 2) above, as well as the right of THE BUYER to deposit in its own name any patent applications of THE PRODUCT with the competent departments of all the countries of THE CONTRACTUAL TERRITORY, defined in Article 3 of this agreement, which are not included in the list of those detailed in Recital 2).

c) All the information and documents related to the patent and THE PRODUCT, independently of its place of issue.

d) The right of THE BUYER to carry out as many activities and to perform as many steps it may deem necessary in order to make tests, experiences and/or trials tending to reach the final development of THE PRODUCT, so that THE PRODUCT be finally fit for Human application purposes. To this end, THE BUYER will be entitled to enter into a partnership with any corporation or laboratory or to demand technical advice and/or assistance to whom it may deem necessary. The results of said tests, experiences and/or trials, if any, will be immdiately noticed to THE SELLER, who will use them in order to reach as soon as possible an upper stage of development of THE PRODUCT, as stated in Recitals 5) and 6) of the present agreement, that is to say, the results of the tests, experiences and/or trials carried out by THE BUYER, whether by its own or within a

partnership, will fully revert to THE SELLER, exclusively in Spain and for the sole purpose of accelerating the attainment of the fourth stage of development of THE PRODUCT.

The results of the experiences, tests and/or trials, as stated in the present stipulation, may be utilized by THE BUYER, within the territory detailed in Article 3, for the recording in the Health Register of THE PRODUCT or for whatever purposes it may deem appropriate or necessary.

The expenses THE BUYER may incur if entering into a partnership or when carrying out the tests, experiences and/or trials will be on its own account.

Article 3. TERRITORY

THE BUYER shall have the exclusive right to freely dispose of the patent and THE PRODUCT and to carry out experiences, tests and/or trials on THE PRODUCT, as stated in the precedent Article in all the countries of the world (hereinafter THE CONTRACTUAL TERRITORY) from which Spain is excluded. Within THE CONTRACTUAL TERRITORY, THE BUYER will be able to transfer, sell or dispose of the patent and THE PRODUCT, without any limitation whatsoever, to grant as many licenses as it may deem convenient or necessary, to enter into partnerships for the development of THE PRODUCT and to request in its own name from the competent departments of the countries of THE CONTRACTUAL TERRITORY as many patent applications it may deem necessary or convenient. For its part, THE SELLER will not be authorized either to use THE PRODUCT within THE CONTRACTUAL TERRITORY or to grant licenses for its production.

THE BUYER will receive the ownership of patent of THE PRODUCT for the manufacture, distribution and commercialization of THE PRODUCT, either directly or indirectly, throughout THE CONTRACTUAL TERRITORY.

Consequently, THE BUYER will not have any right over the patent of THE PRODUCT in Spain where THE SELLER keeps for itself the full ownership of the patent of THE PRODUCT, of the exclusive right of its manufacturing procedure, of the results of the experiences, tests and/or trials carried out by THE BUYER within THE CONTRACTUAL TERRITORY, as well as any other industrial property rights,

including the experiments and trials, related documents, know-how and secret formulae for the production, distribution and sale of THE PRODUCT, in accordance with Article 9.

Article 4. PATENT APPLICATIONS

THE SELLER, undertakes to submit, when necessary, to the competent departments of the countries listed in Recital 2) the corresponding applications so that the patents applied for are granted to THE BUYER and not to THE SELLER. All expenses relating to the patent applications in the context of the registration of the patents in the name of THE BUYER will be borne by the latter.

Article 5. QUANTITY AND KNOWLEDGE OF THE PRODUCT

The BUYER hereby states that it knows and is acquainted with the current state of development of THE PRODUCT, as well as its effects and applications.

Consequently, and in virtue of said knowledge, THE BUYER will not make any claim whatsoever to THE SELLER in connection with the manufacturing procedure or any aspect derived from THE PRODUCT or from its final results.

At THE BUYER's request, THE SELLER assumes the responsibility for carrying out a technical control of the manufacturing procedure of THE PRODUCT and guarantees that THE PRODUCT is suitable for the purposes for which it was invented, taking for granted that THE BUYER and licensees will adequately use its manufacturing procedure.

The SELLER will not be held liable for eventual modifications in the manufacturing procedure of THE PRODUCT introduced by THE BUYER or the persons or entities to which THE BUYER grants licenses, or for the harmful side effects which such modifications could eventually cause.

Article 6. PRICE

The selling price of the patent of THE PRODUCT and its rights is established as follows:

Troisième feuillet

a) TWENTY FIVE MILLION PESETAS (25.000.000 Ptas.) once THE PRODUCT has satisfactorily reached stage I of its development, as stated in Recital 5) of the present agreement.

b) TWENTY FIVE MILLION PESETAS (25.000.000 Ptas.) once THE PRODUCT has satisfactorily reached stage II of its development, as stated in Recital 5) of the present agreement.

c) THIRTY FIVE MILLION PESETAS (35.000.000 Ptas.) once THE PRODUCT has satisfactorily reached stage III of its development, as stated in Recital 5) of the present agreement.

d) FIFTEEN MILLION PESETAS (15.000.000 Ptas.) upon recording in the Health Register of THE PRODUCT in the CONTRACTUAL TERRITORY.

Both parties expressly state that there is a fair and perfect equivalence between the patent of THE PRODUCT and remaining rights stemming from it, which are the subject matter of this agreement and the agreed price, and they expressly waive any action and/or defence which would invalidate the legal effects of this agreement.

Article 7. Lack of payment

It is expressly agreed that if the BUYER does not comply with this agreement and, in particular, should THE BUYER fail to pay the agreed price and/or the agreed royalties at the appointed time, the SELLER will have the right to demand, at its own judgement, either the performance of the agreement or its cancellation, with damages in both cases, by means of a simple written notice with recorded delivery. In case of cancellation of this agreement, ownership, and thus the use and remaining rights inherent to the property of the patent of THE PRODUCT, subject matter of this Agreement, shall fully revert to the SELLER. In such an event, THE BUYER shall have no right to claim from the SELLER any compensation whatsoever and/or reimbursement of any amounts or royalties received.

Article 8. TITLE

The SELLER expressly states that the patent applications listed in Recital 2) of the

present agreement are free from any and all liens, encumbrances, attachments and, in general, from any court or out of court measures which might have in any way restricted the property and free disposal rights of the patent of THE PRODUCT.

Article 9. OBLIGATION TO PRODUCE

The BUYER undertakes to produce, distribute and sell THE PRODUCT in the CONTRACTUAL TERRITORY within two years from the date that the production of THE PRODUCT begins in Spain, unless it is prevented from doing so by the legislation of any of the relevant countries included in THE CONTRACTUAL TERRITORY.

The BUYER shall permit the sale of THE PRODUCT by THE SELLER in those countries belonging to the CONTRACTUAL TERRITORY where THE BUYER has not started commercializing THE PRODUCT in the said term.

Article 10. IMPROVEMENTS

The parties mutually agree to inform each other of any improvements introduced in the manufactoring procedure of THE PRODUCT. The BUYER undertakes to impose such an obligation on any third parties to whom it eventually grants a licence to use the patent of THE PRODUCT or the use of the patents granted so that all third parties keep THE SELLER duly informed of such improvements. The BUYER further undertakes to impose on such third parties the duty of sending to THE SELLER copies of all booklets, brochures, medical information and any other explanations that such third parties may give or print in relation to THE PRODUCT and/or the patents already granted.

The improvements shall be considered to be the property of the party making the improvement, but said party shall offer THE BUYER, at no cost for the latter, any information on such improvements. THE BUYER shall include in its license agreements with third parties their obligation to furnish all information and documents available on the improvement(s) to THE SELLER as set forth in the foregoing paragraph.

The party making the improvement, of whatever kind, shall grant at no cost to THE BUYER and THE SELLER, if any of these is a third party

or, whatever the case may be, is any among themselves, a licence to use the patentable procedures and improvements during a ten year period.

Article 11. SECRECY

The BUYER agrees to keep secret the contents of the patent of THE PRODUCT which is the subject matter of this agreement and the related documents and information provided by THE SELLER. The BUYER shall also take the appropriate measures to restrict access to the contents of such PRODUCT to the smallest possible number of collaborators.

Should THE BUYER license or in any other manner dispose of the patent of THE PRODUCT, its documents or information in favour of third parties, THE BUYER undertakes to impose the secrecy obligation on these third parties as provided herein and, furthermore, THE BUYER undertakes to keep THE SELLER advised of these transfers.

Article 12. MISCELLANEOUS CONDITIONS

The invalidation of any of the provisions of this Agreement will not entail the invalidation of the remaining provisions, as long as the nature of the Agreement and the essential terms therein remain unaffected.

Any amendments or additions to this Agreement shall be introduced in writing. The parties will only recognize as valid, in performing this Agreement, those communications made in writing to the domiciles mentioned in Article 14 of this Agreement.

Article 13. REGISTER

THE SELLER undertakes to provide all the necessary means to THE BUYER so that ownership over the patent of THE PRODUCT is registered in THE BUYER's name at all competent departments of THE CONTRACTUAL TERRITORY. In turn, THE BUYER engages itself, as stated in Article 2, to immediately notice THE SELLER of the results of all tests, experiences and/or trials carried out in THE CONTRACTUAL TERRITORY. All expenses connected with patent applications in favour of THE BUYER within THE CONTRACTUAL TERRITORY and, as the case may be, those connected with the reversion of the ownership to THE SELLER in case of non-fulfilment and cancellation of

this agreement attributable to THE BUYER, will be borne by the latter

Article 14. LANGUAGE, DOMICILE, JURISDICTION AND ARBITRATION

For any communication or notice required or permitted hereunder, the parties establish their domicile as follows:

THE SELLER: Crta. de Valencia, Km 23, Arganda del Rey, Madrid, España.

THE BUYER: 8, rue Zithe, Luxembourg, Grand Duchy of Luxembourg.

This Agreement will be performed and construed according to the laws of Luxembourg.

Any dispute between the parties stemming from the interpretation or performance of this Agreement which cannot be solved amicably will be referred, without recourse to ordinary or commercial courts, to the arbitration of the International Chamber of Commerce at The Hague, in accordance with the rules and procedures of the said Chamber, whose award shall be final and binding for the parties.

Article 15. TRANSFER TO THIRD PARTIES

EUROFIN is entitled to sell the patent of THE PRODUCT and its rights to manufacture, distribute and commercialize THE PRODUCT or to transfer to third parties its rights and obligations stemming from this agreement within THE CONTRACTUAL TERRITORY.

EXPENSES

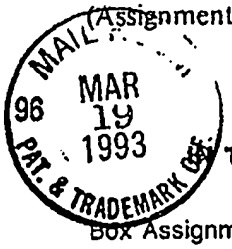
The expenses, costs, fees and charges of any kind whatsoever, which fall to be paid by THE BUYER as a result of this document, amount approximately to 100.000.-LUF.

The undersigned notary who knows English, states herewith that at the request of the persons appearing, the present notarial deed is worded in English, followed by a French version; on request of the persons appearing and in case of divergences between the English and French text, the English version will be binding.

Cinquième feuillet

120-581 D

(Assignment (Document) Cover Sheet [16-6] —page 1 of 8)



PATENT

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: *"Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C 20231, unless they are filed together with new applications or with a petition under § 3.81(b)." 37 CFR 3.27.*

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: *"A cover sheet may not refer to both patents and trademarks." 37 CFR 3.31(b).*

Attached please find an assignment (document) for recordal.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this "Assignment (Document) Cover Sheet (along with any paper referred to as being attached or enclosed) is being deposited on the date shown below with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(check and complete appropriate item below):

37 CFR 1.8(a)
☒ with sufficient postage as first class mail

or

37 CFR 1.10
☐ as "Express Mail Post Office to Addressee" Mailing Label No.

Michelle M. Velotta
(Type or print name of person mailing paper)

Date March 17, 1993

Michelle M. Velotta
(Signature of person mailing paper)

FEE 64.57 FEB 22 93

160 AT 04/05/93 07578942 1 581 120.00 CK

916682?3

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 CFR 3.21 and 37 CFR 3.31(a)(4))

NOTE: *"An assignment relating to a patent must identify the patent by the patent number. An assignment relating to a national patent application must identify the national patent application by the application number (consisting of the series code and the serial number, e.g., 07/123,456) or the serial number and the filing date. An assignment relating to an international patent application which designates the United States of America must identify the international application by the international application number (e.g., PCT/US90/01234)." 37 CFR 3.21.*

1. This assignment is for the following patent application and/or issued patent:

National application: SN: 0 7 /578,942 filed on September 7, 1990
International application: PCT/ /
Patent No: Issued: ***

(complete if applicable) which was previously assigned on August 6, 1991
Reel 5791
Frame 570

(also complete the following, if applicable) Subsequent Assignment has been filed, but not yet recorded.

☒ and also for the applications and/or patents shown on the attached list of FURTHER APPLICATION(S) and/or PATENT(S) BEING ASSIGNED

Number of pages added 1

***Inventors: Calatayud, Jose
Conde, Jose Ramon

Title: New Pregna-1, 4-Diene-3, 20-Dione-16-17-Acetal-21 esters, Process for Their Preparation, Composition, and Methods for the Treatment of Inflammatory Conditions

REEL 6467 FRAME 224

(Assignment (Document) Cover Sheet [16-6] —page 3 of 8)

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE (37 CFR 3.28(a)(6))

(4) A. The total number of applications and/or patents identified in this cover sheet is 3.

B. The total fee is (37 CFR 1.21(h)):

3 x $40.00 = $120.00

Total number of applications and/or patents

(7) C. Payment of fee is made by;

☒ attached check for $120.00

☐ please charge Account _____

the sum of $_____

A duplicate of this cover sheet is attached

Please charge Account 06-0308 for any fee deficiency or credit to account any overpayment.

NAME OF PARTY(IES) CONVEYING INTEREST (37 CFR 3.31(a)(1))

(1) 3. The party(ies) conveying interest is (are):

Name 1: EUROFIN S.A.

Name 2:

Name 3:

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST (37 CFR 3.31(a)(2))

(2) 4. The rights are being conveyed to:

Name: Enrique Elias Laroza

Address: Avela, San Felipe 758

Lima, Peru

REEL 5457 FRAME 225

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 CFR 3.31(a)(3))

(3) 5. The accompanying document intends to accomplish:

- [X] an assignment 01
- [ ] a security agreement
- [ ] a merger
- [ ] a license
- [ ] a change of name
- [ ] a change of address
- [ ] other

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 CFR 3.31(a)(5))

(5) 6. Please address correspondence to:

Name: Richard J. Minnich
Address: 1100 Superior Avenue, Suite 700
Cleveland, Ohio 44114-2518
Telephone No.: (216) 861-5582

Fay, Sharpe, Beall, Fagan, Minnich & McKee

(Assignment (Document) Cover Sheet [16-6] —page 5 of 8)

DATE ASSIGNMENT (DOCUMENT) EXECUTED (37 CFR 3.31(a)(7))

(3) 7. The attached assignment (document) was executed on December 17, 1992.
(date)

LANGUAGE OF ASSIGNMENT (DOCUMENT) TO BE RECORDED

NOTE: "The Office will accept and record non-English language documents only if accompanied by a verified English translation signed by the individual making the translation." 37 CFR 3.26.

8. The attached document:

XX ☒ is in the English language

☐ is not in the English language and a verified English translation signed by the individual making the translation is attached.

ORIGINAL DOCUMENT OR TRUE COPY SUBMITTED

NOTE: "Either the original document or a true copy of the original document may be submitted for recording. Only one side of each page shall be used. The paper used should be flexible, strong, white, non-shiny, durable, and preferably no larger than 21.6 x 33.1 cm. (8 1/2 x 14 inches) with a 2.5 cm. (one-inch) margin on all sides." 37 CFR 3.24.

9. Submitted herewith is:

☐ the original document

XX ☒ a true copy of the original document

REEL 6467 FRAME 227

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF ADDRESS

(check item if applicable)

10. ☐ Since the purpose of the attached documents is to record a change of address of the assignee the particulars of the previously recorded assignments for each application and/or patent are shown.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF NAME

(check item if applicable)

11. ☐ Since the purpose of the attached documents is to record a change of name of the assignee the particulars of the previously recorded assignments for each application and/or patent are shown.

CHANGE OF PATENT MAINTENANCE FEE ADDRESS

(check item if applicable)

12. ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent to the Office separately.

(Assignment (Document) Cover Sheet [16-6] —page 7 of 8)

STATEMENT (37 CFR 3.31(a)(9)) AND SIGNATURE 37 CFR 3.31(a)(10))

(9) To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Date: 3/12/93

(Name of party submitting document)

(Signature of party submitting document)

Richard J. Minnich

SIGNATURE OF ATTORNEY

Reg. No. 24,175

Tel. No. (216) 861-5582

Richard J. Minnich

Type or print name of Attorney

1100 Superior Avenue, Suite 700

P.O. Address

Cleveland, Ohio 44114-2518

Fay, Sharpe, Beall, Fagan, Minnich & McKee

REEL 6467 FRAME 229

ASSIGNMENT (DOCUMENT) COVER SHEET [16-6]
— ADDED PAGE 1)

FURTHER APPLICATION(S) AND/OR PATENTS BEING ASSIGNED		DETAILS OF PRIOR RECORDAL (IF ANY)
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	
For:	/	
XX Patent: 4,812,482	Issued: March 14, 1989	
Inventors: Montaro, Fernando; Calatayud, Jose; Luna, Manuel		
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
XX Patent: 3,982,002	Issued: September 21, 1976	
Inventors: Montaro, Fernando; Vila-Coro, Antonio; Calatayud, Jose		
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	

ADD ADDITIONAL PAGE FOR FURTHER APPLICATION(S) AND/OR PATENT(S) BEING ASSIGNED

(20) 1100

92/8 (4)

40

PUBLIC DEED

In the town of Vaduz, Principality of Liechtenstein, on the 17th of December 1992

before me, Egon Seger, Judge of Peace and Public Officer

G A T H E R E D

On the one hand, Mr. Tobias Hauser, of age, of Swiss nationality, with domicile in Talacker 35, 8001 Zurich, Switzerland, who's identity I have checked,

exposing that

he is acting on behalf and representation of EUROFIN S.A., a company organised and existing under the laws of Luxembourg, domiciled in 8, Rue Zithe - Luxembourg, which hereinafter shall be referred to as the GRANTOR,

and,

On the other hand, Mr. Enrique Elias Laroza, of age, of Peruvian nationality, with domicile in Lima (Peru), Avda. San Felipe 758, in possession of Peruvian Passport number 1471043, who's identity I have checked,

exposing that

he acts in his own name and behalf, hereinafter the GRANTEE.

REEL 6457 FRAME 231

THIS BEING, THE PARTIES JOINTLY, AND, WHERE SO QUOTED, INDIVIDUALLY, MAKE THE FOLLOWING DECLARATION:

Mr. Hauser assures that he has the required legal capacity to validly act in the name and representation of the GRANTOR and to execute this document. Under this statement and mutually recognising each other's capacity and

C O N S I D E R I N G

1. That the GRANTOR and the GRANTEE entered into an agreement dated July 17th 1992, by means of which the GRANTOR granted to the GRANTEE a first refusal right to acquire the full and exclusive ownership of the following patents, patent applications and trademarks, in the following countries:

A) Patent registered under the name "FEPRADINOL. HCI", which chemical structure is "Bencenometanol, a [[(2 - hidroxi - 1.1. - dimotiil etil)

VERMITTLERAMT FL-9490 VADUZ

aminol] metil] clorhidrate (67704-50-1) (C12 H19 NO2 HCl), in the following countries and under the following registration numbers:

- BELGIUM: Patent nº 903.651.
- FRANCE: Patent nº 2.573.071.
- SWITZERLAND: Patent nº 670.823.
- ITALY: Patent nº 1.184.670.
- U.S.A.: Patent nº 4.812.482.
- PORTUGAL: Patent nº 81.479.
- JAPAN: Patent application nº 60-249.089.

B) Patent registered under the name "2 Vincamine Cetoglutarate", the chemical structure of which is "Bi-2-oxo-1,5 Vincamine Pentanodioicate", in the following countries and under the following registration numbers:

- U.S.A.: Patent nº 3982002.
- BELGIUM: Patent nº 823806.
- GERMANY: Patent nº P-2500599-6-09.
- LUXEMBOURG: Patent nº 71545.
- SWITZERLAND: Patent nº 593974.
- FRANCE: Patent nº 7430299 (2283669).
- JAPAN: Patent nº 1093823.

C) Patent application under the name "CICLESONIDE", in the following countries and under the following application numbers:

- FRANCE: Application nº 91 10682.
- ITALY: Application nº 91A002296.
- UNITED KINGDOM: Application nº 9118967.0.
- GERMANY: Application nº P41295358.
- GREECE: Application nº 910100353.

- PORTUGAL: Application nº 98897.
- NETHERLANDS: Application nº 9101472.
- BELGIUM: Application nº 9100816.
- LUXEMBOURG: Application nº 88001.
- JAPAN: Application nº 227418.
- AUSTRALIA: Application nº 8368691.
- SWITZERLAND: Application nº 02619-913.

R.O.C.: Application nº 15617/91.

- CANADA: Application nº 2.050.812-4.
- AUSTRIA: Application nº A1769/91.
- U.S.A.: Application nº 578942.

D) Trademark "CETOVINCA", in the following countries an under the following registration numbers:

- BENELUX: Trademark nº 334058.
- GERMANY: Trademark nº 951540.
- FRANCE: Trademark nº 920766.
- ITALY: Trademark nº 321876.
- SWITZERLAND: Trademark nº 279288.

E) Trademark "OXOVINCA", in the following countries and under the following registration numbers:

- GERMANY: Trademark nº 963183.
- FRANCE: Trademark nº 924576.
- ITALY: Trademark nº 321877.
- SWITZERLAND: Trademark nº 279289.

2. That when entering into the agreement dated July 17th 1992, the GRANTOR was still negotiating the acquisition of the patent application known under the name CICLESONIDE.

3. That the GRANTOR has finally acquired the full and exclusive ownership of said patent application on December 3rd, 1992.

4. That within the term of one year as from the date of signature of the agreement dated July, 17th 1992, and prior notice from the GRANTEE to the GRANTOR, the GRANTEE executes the first refusal right according to the following

STIPULATIONS

FIRST

The GRANTEE will pay to the GRANTOR, within the term of one year as from the date of signature of the present agreement, the sum of 630 million pesetas and therefore acquires as from December 17th, 1992, the full and exclusive ownership of the patents, patent application and trademarks described in Considerings A), B), C), D) and E) to this agreement, in all the countries in which said patents and trademarks are registered or in which the patent applications have been applied for registration, being then entitled to register them in his name.

SECOND

All costs and expenses related to the formalization of the present agreement, such as notary's fees, all related taxes and registration fees of all patents, patent applications and trademarks will be borne by the GRANTEE.

THIRD

This document is drawn in two original copies, both in english, both texts having identical validity and effects.

For any communication or notice envisaged hereunder, the parties establish their domicile as follows:

THE GRANTOR: 8, Rue Zithe, Luxembourg.

THE GRANTEE: Avda. San Felipe 758, Lima, Peru.

FOURTH

This agreement is performed and construed according to the Laws of Luxembourg.

Any dispute arising from the interpretation or performance of the present

agreement which could not have been solved amicably will be referred, without recourse to ordinary or commercial Courts, to arbitration of the International Chamber of Commerce of The Hague, in accordance with said Chamber's rules of procedure, whose award shall be final and binding for the parties.

In witness thereof the parties have signed this agreement as of the place and date first above written and I add my own signature and stamp.

The declaration of the parties have been duly translated to me by Ms. Christel Gstöhl, also present.

In Witness

Vaduz, December 17, 1992

VERMITTLERAMT FL-9490 VADUZ

Egon Seger
Judge of Peace

Tobias Hauser

Enrique Elias Laroza

Laut Beglaubigungsregister Nr. 261
haben die persönlich bekannten
Hr. Tobias Hauser Lärchen 35, Triesen
Hr. Enrique Elias Laroza, Lima/Peru
Adr: San Felipe 758
vorstehende Unterschriften eigenhändig vor mir beigesetzt (als die ihrige anerkannt).

Vermittleramt
VADUZ, am 17. Dez. 1992

STEMPEL-MARKE 10 Fr
VERMITTLERAMT FÜRSTENTUM LIECHTENSTEIN
FÜRSTENTUM LIECHTENSTEIN Fr. 2 Fr. STEMPELMARKE
FÜRSTENTUM LIECHTENSTEIN Fr. 2 Fr. STEMPELMARKE

Declaration:

According to art. 84 of the RSO of the Principality of Liechtenstein, (official bulletin nr. 8. 1923) the afore mentioned declarations are translated to me because the english language is not known to me. The present translator according to art. 84 par. 2 of the RSO (official bulletin nr. 8. 1923) hereby declares that the translation has been made consciously.

Erklärung:

Gemäss Art. 84 der liechtensteinischen RSO (Landesgesetzblatt 1923, No. 8) wird mir die obige Erklärung übersetzt, da ich der englischen Sprache nicht mächtig bin. Der beigezogene Uebersetzer erklärt hiermit gemäss Art. 84 Abs. 2 der RSO (Landesgesetzblatt 1923, No. 8), dass die Uebersetzung gewissenhaft erfolgt ist.

Vaduz, December 17, 1992

Der Uebersetzer/The Translator:

Christel Gstöhl

Beglaubigungsregister Nr. 2164

Die Echtheit der Unterschrift von
Frl. Christel Gstöhl
Schaan, Im Kresta 30
wird bestätigt.

Vaduz, den 17. Dez. 1992

VERMITTLERAMT VADUZ

FÜRSTENTUM LIECHTENSTEIN STEMPELMARKE Fr. FL-9490 VADUZ

Gebührenbemessungsgrundlage:

Maximalsatz gemäss Art. 42 lit a
LGBL. 1974 Nr. 42 i.d.g.F.

sFr. 5'000.--

VERMITTLERAMT FL-9490 VADUZ

REEL 6467 FRAME 236

BP 0102178

(7)

PROCURATION

La société EUROFIN S.A., ayant son siège social à Luxembourg, 8, rue Zithe (ci-après la "Société"), ici représentée par M. René Diederich, Administrateur et M. Tom Loesch, Administrateur

donne pouvoir

à Maîtres Vital Hauser et Tobias Hauser, avocats, demeurant tous deux à Zürich, Talacker 35, afin que l'un quelconque d'eux, chacun sous sa signature isolée, puisse accomplir au nom et pour compte de la Société, les actes et démarches suivantes :

1) Faire toutes les démarches nécessaires et signer pour elle et en son nom tous documents en relation avec la cession de la demande de brevet et du brevet "CICLESONIDE" et de tous droits de propriété industrielle et intellectuelle y afférents, au prix et aux conditions à arrêter par eux, dans les pays énoncés ci-dessous, entre la société de droit luxembourgeois EUROFIN S.A. comme partie cédante et toute personne physique ou morale que les mandataires jugent convenable, comme partie cessionnaire, et concéder des options d'achat sur ladite demande de brevet et ledit brevet en faveur de toute personne physique ou morale, dans les pays suivants :

- France : demande de brevet no. 91 10682.
- Italie : demande de brevet no. 91A002296.
- Royaume Uni : demande de brevet no. 9118967.0.
- Allemagne : demande de brevet no. P41295358.
- Grèce : demande de brevet no. 910100353.
- Portugal : demande de brevet no. 98897.
- Pays-Bas : demande de brevet no. 9101472.
- Belgique : demande de brevet no. 9100816.
- Luxembourg : demande de brevet no. 88001.
- Japon : demande de brevet no. 227418.
- Australie : demande de brevet no. 8368691.
- Suisse : demande de brevet no. 02619-913.
- R.O.C. : demande de brevet no. 15617/91.
- Canada : demande de brevet no. 2.050.812-4.
- Autriche : demande de brevet no. A1769/91.
- Etats-Unis : demande de brevet no. 578942.

2) Faire toutes les démarches nécessaires et signer pour elle et en son nom tous documents en relation avec la cession du brevet "2 VINCAMINE CETOGLUTARATE" et de tous droits de propriété industrielle et intellectuelle y afférents, au prix et aux conditions à arrêter par eux, dans les pays énoncés ci-dessous, entre la société de droit luxembourgeois EUROFIN S.A. comme partie cédante et toute personne physique ou morale que les

REEL 6467 FRAME 237

VERMITTLERAMT FL-9490 VADUZ

BP 0102181

(8)

mandataires jugent convenable, comme partie cessionnaire, et concéder des options d'achat sur ledit brevet en faveur de toute personne physique ou morale dans les pays suivants, où le brevet a été enregistré au nom de EUROFIN S.A. :

- Etats-Unis : brevet no. 3982002.
- Belgique : brevet no. 823806.
- Allemagne : brevet no. P-2500599-6-09.
- Luxembourg : brevet no. 71545.
- Suisse : brevet no. 593974.
- France : brevet no. 7430299 (2283669).
- Japon : brevet no. 1093823.

3) Faire toutes les démarches nécessaires et signer pour elle et en son nom tous documents en relation avec la cession de la demande de brevet et du brevet "FEPRADINOL HCl" et de tous droits de propriété industrielle et intellectuelle y afférents, au prix et aux conditions à arrêter par eux, dans les pays énoncés ci-dessous, entre la société de droit luxembourgeois EUROFIN S.A. comme partie cédante et toute personne physique ou morale que les mandataires jugent convenable, comme partie cessionnaire, et concéder des options d'achat sur ladite demande de brevet et ledit brevet en faveur de toute personne physique ou morale dans les pays suivants, où le brevet est enregistré au nom de EUROFIN S.A. :

- Belgique : brevet no. 903.651.
- France : brevet no. 2.573.071.
- Suisse : brevet no. 670.823.
- Italie : brevet no. 1.184.670.
- Etats-Unis : brevet no. 4.812.482.
- Portugal : brevet no. 81.479.
- Japon : demande de brevet no. 60-249089.

4) Faire toutes les démarches nécessaires et signer pour elle en son nom tous documents en relation avec la cession des marques "CETOVINCA" et "OXOVINCA" et de tous droits de propriété industrielle et intellectuelle y afférents, au prix et aux conditions à arrêter par eux, dans les pays énoncés ci-dessous, entre la société de droit luxembourgeois EUROFIN S.A. comme partie cédante et toute personne physique ou morale que les mandataires jugent convenable, comme partie cessionnaire, et concéder des options d'achat sur lesdites marques en faveur de toute personne physique ou morale dans les pays suivants, où elles sont enregistrées au nom de EUROFIN S.A. :

- Marque CETOVINCA no. 334058 (Benelux).
- Marque CETOVINCA no. 951540 (Allemagne).
- Marque CETOVINCA no. 920766 (France).
- Marque CETOVINCA no. 321876 (Italie).
- Marque CETOVINCA no. 279288 (Suisse).
- Marque OXOVINCA no. 963183 (Allemagne).

- Marque OXOVINCA no. 924576 (France).
- Marque OXOVINCA no. 321877 (Italie).
- Marque OXOVINCA no. 279289 (Suisse).

5) Recevoir au nom de la Société le prix payé pour la vente des brevets et marques ou pour la concession de ou des options, ouvrir un compte bancaire au nom de la Société auprès de tout établissement de crédit afin d'y déposer les montants ainsi reçus au nom de la Société et donner toutes instructions nécessaires en relation avec ce compte bancaire.

6) Aux effets ci dessus, signer et déposer toutes pièces, verser toute taxe exigible, élire domicile, remplir toutes formalités légales, retirer l'expédition du procès-verbal de transfert et, en général, faire aux fins indiquées ci-dessus tout ce qui sera requis dans les différents cas qui peuvent se présenter, promettant l'avoir pour agréable et le ratifiant d'avance.

Luxembourg, le 13 octobre 1992

Tom Loesch
Administrateur

René Diederich
Administrateur

L E G A L I S A T I O N

Vu pour légalisation des signatures de Messieurs Tom LOESCH et René DIEDERICH, personnellement connus du notaire soussigné.

Luxembourg-Eich, le 15 octobre 1992

A0162Rnd

BP 0102221

VERMITTLERAMT FL-9490 VADUZ

(10)

APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. Pays: Grand Duché de Luxembourg

Le présent acte public

2. a été signé par Me Joseph Verdicon

3. agissant en qualité de Notaire

4. est revêtu du sceau/timbre de

Attesté

5. à Luxembourg 6. le 19 OCT. 1992

7. par Ministère des Affaires Etrangères

8. sous N° 2230 A/92

9. Sceau/timbre: 10. Signature:

Bernard BACH

Préposé

Visas et Légalisations

El presente folio es el agregado al documento en el que figura la firma de D. /Dª José Manuel Rodríguez-Cepeda García de fecha 3 Febrero 1993

Apostille (o legalización única)
(Convention de La Haye du 5 octobre 1961)
(Real Decreto 2433/1978, de 2 de octubre)

1. **País:** *España*
   El presente documento público
2. Ha sido firmado por D. José Manuel Rodríguez-Cepeda Sánchez
3. Actuando en calidad de *NOTARIO*
4. Se halla sellado/timbrado con *el de su Notaría*

CERTIFICADO

5. En Madrid 6. El 5 Febrero de 1993
7. Por el Decano del Colegio Notarial de Madrid
8. Con el número 55193
9. Sello/timbre: 10. Firma:

D José María Lucena Conde
Miembro de la Junta Directiva en funciones de Decano

SELLO DE LEGALIZACIONES
25
VEINTICINCO PESETAS

MAR 19 93
RECORDED
PATENT AND TRADEMARK OFFICE

REEL 6467 FRAME 241

BW 0205315

20. 0-581

(Assignment (Document) Cover Sheet [16-6] —page 1 of 8)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: *"Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C. 20231, unless they are filed together with new applications or with a petition under § 3.81(b)." 37 CFR 3.27.*

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: *"A cover sheet may not refer to both patents and trademarks." 37 CFR 3.31(b).*

Attached please find an assignment (document) for recordal.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this "Assignment (Document) Cover Sheet (along with any paper referred to as being attached or enclosed) is being deposited on the date shown below with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(*check and complete appropriate item below*):

XX 37 CFR 1.8(a) with sufficient postage as first class mail

or

☐ 37 CFR 1.10 as "Express Mail Post Office to Addressee" Mailing Label No._____

Michelle M. Velotta
(Type or print name of person mailing paper)

Date March 19, 1993

(Signature of person mailing paper)

REEL 6464 FRAME 548

060 JM 04/05/93 07578942 1 591 120.00 CK

91668384

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 CFR 3.21 and 37 CFR 3.31(a)(4))

NOTE: *"An assignment relating to a patent must identify the patent by the patent number. An assignment relating to a national patent application must identify the national patent application by the application number (consisting of the series code and the serial number, e.g., 07/123,456) or the serial number and the filing date. An assignment relating to an international patent application which designates the United States of America must identify the international application by the international application number (e.g., PCT/US90/01234)." 37 CFR 3.21.*

1. This assignment is for the following patent application and/or issued patent:

National application: SN: 07 / 578,942 filed on September 7, 1990
International application: PCT/ /
Patent No: Issued: ***

(complete if applicable) which was previously assigned on August 6, 1991
Reel 5791
Frame 570
Subsequent Assignments have been filed, but not yet recorded.

(also complete the following, if applicable)

☐ and also for the applications and/or patents shown on the attached list of FURTHER APPLICATION(S) and/or PATENT(S) BEING ASSIGNED

Number of pages added _____

***Inventors: Calatayud, Jose
Conde, Jose Ramon
Luna, Manuel

Title: New Pregna-1, 4-Diene-3, 20-Dione-16-17-Acetal-21 esters, Process for Their Preparation, Composition, and Methods for the Treatment of Inflammatory Conditions

REEL 5791 FRAME 570

(Assignment (Document) Cover Sheet |16-6| —page 3 of 8)

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE (37 CFR 3.28(a)(6))

A. The total number of applications and/or patents identified in this cover sheet is 3

B. The total fee is (37 CFR 1.21(h)):

3 x $40.00 = $120.00

Total number of applications and/or patents

C. Payment of fee is made by;

☒ attached check for $120.00

☐ please charge Account _____

the sum of $_____

A duplicate of this cover sheet is attached

Please charge Account 06-0308 for any fee deficiency or credit to account any overpayment.

NAME OF PARTY(IES) CONVEYING INTEREST (37 CFR 3.31(a)(1))

3. The party(ies) conveying interest is (are):

Name 1: Enriquie Elias Laroza

Name 2:

Name 3:

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST (37 CFR 3.31(a)(2))

4. The rights are being conveyed to:

Name: PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A.

Address: Plaza Valle del Conde Suchil 15

Madrid, Spain

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 CFR 3.31(a)(3))

(3)

5. The accompanying document intends to accomplish:

- [X] an assignment
- [ ] a security agreement
- [ ] a merger
- [ ] a license
- [ ] a change of name
- [ ] a change of address
- [ ] other

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 CFR 3.31(a)(5))

(5)

6. Please address correspondence to:

Name: Richard J. Minnich
Address: 1100 Superior Avenue, Suite 700
Cleveland, Ohio 44114-2518
Telephone No.: (216) 861-5582

Fay, Sharpe, Beall, Fagan,
Minnich & McKee

(Assignment (Document) Cover Sheet [16-6] —page 5 of 8)

DATE ASSIGNMENT (DOCUMENT) EXECUTED (37 CFR 3.31(a)(7))

7. The attached assignment (document) was executed on December 17, 1992.
(date)

LANGUAGE OF ASSIGNMENT (DOCUMENT) TO BE RECORDED

NOTE: "The Office will accept and record non-English language documents only if accompanied by a verified English translation signed by the individual making the translation." 37 CFR 3.26.

8. The attached document:

- [X] is in the English language
- [ ] is not in the English language and a verified English translation signed by the individual making the translation is attached.

ORIGINAL DOCUMENT OR TRUE COPY SUBMITTED

NOTE: "Either the original document or a true copy of the original document may be submitted for recording. Only one side of each page shall be used. The paper used should be flexible, strong, white, non-shiny, durable, and preferably no larger than 21.6 x 33.1 cm. (8 1/2 x 14 inches) with a 2.5 cm. (one-inch) margin on all sides." 37 CFR 3.24.

9. Submitted herewith is:

- [ ] the original document
- [X] a true copy of the original document

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF ADDRESS

(check item if applicable)

10. ☐ Since the purpose of the attached documents is to record a change of address of the assignee the particulars of the previously recorded assignments for each application and/or patent are shown.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF NAME

(check item if applicable)

11. ☐ Since the purpose of the attached documents is to record a change of name of the assignee the particulars of the previously recorded assignments for each application and/or patent are shown.

CHANGE OF PATENT MAINTENANCE FEE ADDRESS

(check item if applicable)

12. ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent to the Office separately.

(Assignment (Document) Cover Sheet [16-6] —page 7 of 8)

STATEMENT (37 CFR 3.31(a)(9)) AND SIGNATURE 37 CFR 3.31(a)(10))

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Date: 3/12/93

(Name of party submitting document)

(Signature of party submitting document)

Richard J. Minnich

SIGNATURE OF ATTORNEY

Reg. No. 24,175

Tel. No. (216) 861-5582

Richard J. Minnich

Type or print name of Attorney

1100 Superior Avenue, Suite 700

P.O. Address

Cleveland, Ohio 44114-2518

Fay, Sharpe, Beall, Fagan,
Minnich & McKee

ASSIGNMENT (DOCUMENT) COVER SHEET [16-6]
— ADDED PAGE 1)

FURTHER APPLICATION(S) AND/OR PATENTS BEING ASSIGNED		DETAILS OF PRIOR RECORDAL (IF ANY)
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	
For:	/	
XX Patent: 4,812,482	Issued: March 14, 1989	
Inventors: Montaro, Fernando; Calatayud, Jose; Luna, Manuel		
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
XX Patent: 3,982,002	Issued: September 21, 1976	
Inventors: Montaro, Fernando; Vila-Coro, Antonio; Calatayud, Jose		
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	

REEL 6194 FRAME 555

ADD ADDITIONAL PAGE FOR FURTHER APPLICATION(S) AND/OR PATENT(S) BEING ASSIGNED

PUBLIC DEED

In the town of Vaduz, Principality of Liechtenstein, on the 17th of December 1992

before me, Egon Seger, Judge of Peace and Public Officer

G A T H E R E D

On the one hand, Mr. Enrique Elias Laroza, of age, of Peruvian nationality, with domicile in Lima (Peru), Avda. San Felipe 758, in possession of Peruvian Passport number 1471043, who's identity I have checked,

exposing that

he is acting in his own name and behalf, hereinafter the GRANTOR,

and,

On the other hand, Mr. Luis Carlos Rodrigo Mazuré, of age, of Spanish nationality, who's identity I have checked

exposing that

he is acting on behalf and representation of PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A. (PROINSER), a company organised and existing under the laws of Spain, domiciled in Plaza Valle del Conde Suchil 15- Madrid, Spain, which hereinafter shall be referred to as the GRANTEE.

THIS BEING, THE PARTIES JOINTLY, AND, WHERE SO QUOTED, INDIVIDUALLY, MAKE THE FOLLOWING DECLARATION:

Mr. Rodrigo assures that he has the required legal capacity to validly act in the name and representation of the GRANTEE and to execute this document under this statement and mutually recognising each other's capacity and

C O N S I D E R I N G

1. That the GRANTOR and the GRANTEE entered into an agreement dated August 19, 1992, by means of which the GRANTOR granted to the GRANTEE a first refusal right to acquire the full and exclusive ownership of the following patents, patent applications and trademarks, in the following countries:

A) Patent registered under the name "FEPRADINOL, HCI", which chemical structure is "Bencenometanol, a [[(2 - hidroxi - 1.1. - dimotiil etil) aminol] metil] clorhidrate (67704-50-1) (C12 H19 NO2 HCI), in the following countries and under the following registration numbers:

RECEIVED: 16 JAN. 1995 FRANKFURT 556

VERMITTLERAMT FL-9490 VADUZ

BP 0102300

- BELGIUM: Patent n° 903.651.
- FRANCE: Patent n° 2.573.071.
- SWITZERLAND: Patent n° 670.823.
- ITALY: Patent n° 1.184.670.
- U.S.A.: Patent n° 4.812.482.
- PORTUGAL: Patent n° 81.479.
- JAPAN: Patent application n° 60-249.089.

B) Patent registered under the name "2 Vincamine Cetoglutarate", the chemical structure of which is "Bi-2-oxo-1,5 Vincamine Pentanodioicate", in the following countries and under the following registration numbers:

- U.S.A.: Patent n° 3982002.
- BELGIUM: Patent n° 823806.
- GERMANY: Patent n° P-2500599-6-09.
- LUXEMBOURG: Patent n° 71545.
- SWITZERLAND: Patent n° 593974.
- FRANCE: Patent n° 7430299 (2283669).
- JAPAN: Patent n° 1093823.

C) Patent application under the name "CICLESONIDE" in the countries and under the numbers listed below:

- FRANCE: Application n° 91 10682.
- ITALY: Application n° 91A002296.
- UNITED KINGDOM: Application n° 9118967.0.
- GERMANY: Application n° P41295358.
- GREECE: Application n° 910100353.
- PORTUGAL: Application n° 98897.

- NETHERLANDS: Application nº 9101472.
- BELGIUM: Application nº 9100816.
- LUXEMBOURG: Application nº 88001.
- JAPAN: Application nº 227418.
- AUSTRALIA: Application nº 8368691.
- SWITZERLAND: Application nº 02619-913.

R.O.C.: Application nº 15617/91.

- CANADA: Application nº 2.050.812-4.
- AUSTRIA: Application nº A1769/91.
- U.S.A.: Application nº 578942.

D) Trademark "CETOVINCA", in the following countries an under the following registration numbers:

- BENELUX: Trademark nº 334058.
- GERMANY: Trademark nº 951540.
- FRANCE: Trademark nº 920766.
- ITALY: Trademark nº 321876.
- SWITZERLAND: Trademark nº 279288.

E) Trademark "OXOVINCA", in the following countries and under the following registration numbers:

- GERMANY: Trademark nº 963183.
- FRANCE: Trademark nº 924576.
- ITALY: Trademark nº 321877.
- SWITZERLAND: Trademark nº 279289.

2. That when entering into the agreement dated August 19, 1992, the GRANTOR had not yet acquired the patent application known under the name CICLESONIDE.

3. That the GRANTOR has finally acquired the full and exclusive ownership of said patent application.

4. That within the term of one year as from the date of signature of the agreement dated August 19, 1992, and prior notice from the GRANTEE to the GRANTOR, the GRANTEE executes the first refusal right according to the following

STIPULATIONS

FIRST

The GRANTEE will pay to the GRANTOR, within the term of one year as from the date of signature of the present agreement, the sum of 639 million pesetas and therefore acquires as from December 17th, 1992, the full and exclusive ownership of the patents, patent application and trademarks described in Considerings A), B), C), D) and E) to this agreement, in all the countries in which said patents and trademarks are registered or in which the patent applications have been applied for registration, being then entitled to register them in his name.

SECOND

All costs and expenses related to the formalization of the present agreement, such as notary's fees, all related taxes and registration fees of all patents, patent applications and trademarks will be borne by the GRANTEE.

THIRD

This document is drawn in two original copies, both in english, both texts having identical validity and effects.

For any communication or notice envisaged hereunder, the parties establish their domicile as follows:

THE GRANTOR: Avda. San Felipe 758, Lima, Peru.

THE GRANTEE: Calle Velazquez 75, Madrid, Spain.

FOURTH

This agreement is performed and construed according to the Laws of Luxembourg.

Any dispute arising from the interpretation or performance of the present agreement which could not have been solved amicably will be referred, without recourse to ordinary or commercial Courts, to arbitration of the International Chamber of Commerce of The Hague, in accordance with said Chamber's rules of procedure, whose award shall be final and binding for the parties.

In witness thereof the parties have signed this agreement as of the place and date first above written and I add my own signature and stamp.

The declaration of the parties have been duly translated to me by Ms. Christel Gstöhl, also present.

In Witness

Vaduz, December 17, 1992

Egon Seger

Judge of Peace

Enrique Elias Laroza

Luis Carlos Rodrigo Mazuré

Laut Beglaubigungsregister Nr. 261
haben die persönlich bekannten
Hr. Enrique Elias Laroza, Lima/Peru
Avda. San Felipe 758
Hr. Luis Carlos Rodrigo Mazuré, Madrid/Spanien
c/o PROINSER, Plaza Valle del Conde Lucha 15
vorstehende Unterschriften eigenhändig vor mir beigesetzt (als die ihrige anerkannt).

Vermittleramt
VADUZ, am 17. Dez. 1992

STEMPEL-MARKE 10 Fr
FÜRSTENTUM LIECHTENSTEIN
VERMITTLERAMT
FÜRSTENTUM LIECHTENSTEIN Fr. 2 Fr. STEMPELMARKE
FÜRSTENTUM LIECHTENSTEIN Fr. 2 Fr. STEMPELMARKE

REEL 6464 FRAME 560

Declaration:

According to art. 84 of the RSO of the Principality of Liechtenstein, (official bulletin nr. 8, 1923) the afore mentioned declarations are translated to me because the english language is not known to me. The present translator according to art. 84 par. 2 of the RSO (official bulletin nr. 8, 1923) hereby declares that the translation has been made consciously.

Erklärung:

Gemäss Art. 84 der liechtensteinischen RSO (Landesgesetzblatt 1923, No. 8) wird mir die obige Erklärung übersetzt, da ich der englischen Sprache nicht mächtig bin. Der beigezogene Uebersetzer erklärt hiermit gemäss Art. 84 Abs. 2 der RSO (Landesgesetzblatt 1923, No. 8), dass die Uebersetzung gewissenhaft erfolgt ist.

Vaduz, December 17, 1992

Der Uebersetzer/The Translator:

Christel Gstöhl

Beglaubigungsregister Nr. 261

Die Echtheit der Unterschrift von
Frl. Christel Gstöhl
Schaan, Im Kresta 30
wird bestätigt.

Vaduz, den 17. Dez. 1992

VERMITTLERAMT VADUZ

FÜRSTENTUM LIECHTENSTEIN STEMPELMARKE Fr. 5 Fr.

FÜRSTENTUM LIECHTENSTEIN STEMPELMARKE Fr.

FL-9490 VADUZ

Gebührenbemessungsgrundlage:

Maximalsatz gemäss Art. 42 lit. a LGBl. 1974 Nr. 42 i.d.g.F.

sFr. 5'000.--

RECORDED FRAMES 1

BP 0102400

(7)

D. Juan Carlos Dulanto Swayne, Secretario del Consejo de Administración de la mercantil "PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A..", domiciliada en Madrid, Plaza Valle del Conde Suchil, 15.

C E R T I F I C O:

Que en la reunión del Consejo de Administración de la sociedad que represento, celebrada en el domicilio social en fecha 9 de diciembre de 1992, con la presencia de la totalidad de los Sres. Consejeros, actuando de Presidente D. Luis Carlos Rodrigo Mazuré y como Secretario, D. Juan Carlos Dulanto Swayne, se adoptaron por unanimidad los siguientes acuerdos:

PRIMERO.- Ratificar en todas sus partes el contrato celebrado por el Presidente del Consejo de Administración, D. Luis Carlos Rodrigo Mazuré, en fecha 19 de agosto de 1992, mediante el cual PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A. adquirió de D. Enrique Elías Laroza, una opción de compra sobre la patente 2 Vincamina Cetoglutarato, sobre la patente Fepradinol, sobre la solicitud de patente Ciclesonide y sobre las marcas Oxovinca y Cetovinca, en ciertos países especificados en el mencionado contrato, y por un precio de 639 millones de pesetas, a pagar en caso de ejecución de dicha opción.

SEGUNDO.- Autorizar al Presidente del Consejo de Administración, D. Luis Carlos Rodrigo Mazuré para que, en nombre y representación de la sociedad, ejecute la mencionada opción de compra, adquiriendo en consecuencia para la sociedad las patentes, solicitud de patente y marcas mencionadas, por el precio de 639 millones de pesetas, pudiendo suscribir al efecto cuantos documentos públicos o privados pudieran ser necesarios sin limitación alguna.

EN FE DE LO CUAL, Y PARA LOS EFECTOS QUE PUDIERAN SER OPORTUNOS, EXTIENDO LA PRESENTE CERTIFICACION, CON EL VISTO BUENO DEL SR. PRESIDENTE, EN MADRID, A LOS ONCE DIAS DEL MES DE DICIEMBRE DE MIL NOVECIENTOS NOVENTA Y DOS.

Luis Carlos Rodrigo

El Presidente
Luis Carlos Rodrigo Mazuré

El Secretario
Juan Carlos Dulanto Swayne

REEL 6164 FRAME 562

VERMITTLERAMT FL-9490 VADUZ

LEGITI.....

BP 0102419

...CIO.- Yo, IGNACIO ZABALA CABELLO, Notario del Ilustre -
Colegio de esta Capital, con residencia en la misma. - -
...E.- Que conozco y reputo legítimas las fir-
mas y rúbricas que anteceden de DON LUIS CA...
LOS RODRIGO MAZURE y DON JUAN CARLOS DULAU...
SMAYNE.- - - - - - - - - - - - - - - - - - -
Madrid, a quince de Diciembre de mil novecien
tos noventa y dos. - - - - - - - - - - - - -

Aplicación Artículo ... Disposición Adicional 3.ª Ley 8/89
DEDUCIBLE IVA CUOTA

Apostille (o legalización única)
(Convención de La Haya de 5 octubre 1961)
(Real Decreto 2433/1978, de 2 de octubre)

1. **País:** *España*
   El presente documento público
2. **Ha sido firmado por** *D. Ignacio Zabala Cabello*
3. **Actuando en calidad de** *NOTARIO*
4. **Se halla sellado/timbrado con** *el de su Notaría*

CERTIFICADO

5. **En** *Madrid* 6. **El** *15-Diciembre 1992*
7. **Por el Decano del Colegio Notarial de Madrid**
8. **Con el número** *53.727*
9. **Sello/timbre:** 10. **Firma:**

D. Carlos Solís Villa
Miembro de la Junta Directiva en funciones de Decano

SELLO DE LEGALIZACIONES
25 PTAS
CINCO PESETAS

VERMITTLERAMT
FL-9490 VADUZ

REEL 6464 FRAME 563

BP 0102439

El presente folio es el agregado al documento en el que figura la firma de D. /Dª D. José Manuel Rodríguez-Escudero Sánchez de fecha 3 de Febrero 1993

Apostille (o legalización única)
(Convention de La Haye du 5 octobre 1961)
(Real Decreto 2433/1978, de 2 de octubre)

1. País: *España*
El presente documento público
2. Ha sido firmado por D. José Manuel Rodríguez-Escudero Sánchez
3. Actuando en calidad de *NOTARIO*
4. Se halla sellado/timbrado con *el de su Notaría*

CERTIFICADO

5. En Madrid 6. El 5 de Febrero 1993
7. Por el Decano del Colegio Notarial de Madrid
8. Con el número 5516
9. Sello/timbre: 10. Firma:

D José María Lucena Conde
Miembro de la Junta Directiva en funciones de Decano

RECORDED
PATENT AND TRADEMARK
OFFICE
MAR 22 1993

REEL 6464 FRAME 564

BW 0205308

120-581

D

(Rel.54-11/92 Pub.603) FORM 16-6 16-27

Assignment (Document) Cover Sheet [16-6] —page 1 of 8)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: *"Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C. 20231, unless they are filed together with new applications or with a petition under § 3.81(b)." 37 CFR 3.27.*

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: *"A cover sheet may not refer to both patents and trademarks." 37 CFR 3.31(b).*

Attached please find an assignment (document) for recordal.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this "Assignment (Document) Cover Sheet (along with any paper referred to as being attached or enclosed) is being deposited on the date shown below with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(check and complete appropriate item below):

☒ 37 CFR 1.8(a) with sufficient postage as first class mail

or

☐ 37 CFR 1.10 as "Express Mail Post Office to Addressee" Mailing Label No.

Michelle M. Velotta
(Type or print name of person mailing paper)

Date

Michelle M. Velotta
(Signature of person mailing paper)

REEL 6578 FRAME 579

91682141

080 KJ 07/06/93 07578942

1 581 120.00 CK

10 Jo

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 CFR 3.21 and 37 CFR 3.31(a)(4))

NOTE: *"An assignment relating to a patent must identify the patent by the patent number. An assignment relating to a national patent application must identify the national patent application by the application number (consisting of the series code and the serial number, e.g., 07/123,456) or the serial number and the filing date. An assignment relating to an international patent application which designates the United States of America must identify the international application by the international application number (e.g., PCT/US90/01234)." 37 CFR 3.21.*

1. This assignment is for the following patent application and/or issued patent:

National application: SN: 0 7 /578,942 filed on September 7, 1990
International application: PCT/ /
Patent No: Issued: ***

(complete if applicable) which was previously assigned/recorded on March 22, 1993
Reel 6464
Frame 0548

(also complete the following, if applicable)

☒ and also for the applications and/or patents shown on the attached list of FURTHER APPLICATION(S) and/or PATENT(S) BEING ASSIGNED

Number of pages added 1

Inventors: Calatayud, Jose
Conde, Jose Ramon
Luna, Manuel

Title: New Pregna-1, 4-Diene-3, 20-Dione-16-17-Acetal-21 Esters Process for Their Preparation, Composition, and Methods for the Treatment of Inflammatory Conditions

(Assignment (Document) Cover Sheet [16-6] —page 3 of 8)

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE (37 CFR 3.28(a)(6))

2. A. The total number of applications and/or patents identified in this cover sheet is 3.

B. The total fee is (37 CFR 1.21(h)):

3 (Total number of applications and/or patents) x $40.00 = $120.00

C. Payment of fee is made by;

☒ attached check for $120.00

☐ please charge Account _____

the sum of $_____

A duplicate of this cover sheet is attached

Please charge Account 06-0308 for any fee deficiency or credit to account any overpayment.

NAME OF PARTY(IES) CONVEYING INTEREST (37 CFR 3.31(a)(1))

(1)

3. The party(ies) conveying interest is (are):

Name 1: Promociones Industriales y Servicios, S.A.

Name 2:

Name 3:

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST (37 CFR 3.31(a)(2))

(2)

4. The rights are being conveyed to:

Name: Elmuquimica Farmaceutica

Address: National Road III, Km. 23

Argana del Rey (Madrid), Spain

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 CFR 3.31(a)(3))

(3)

5. The accompanying document intends to accomplish:

- ☒ an assignment
- ☐ a security agreement
- ☐ a merger
- ☐ a license
- ☐ a change of name
- ☐ a change of address
- ☐ other

19

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 CFR 3.31(a)(5))

(5)

6. Please address correspondence to:

Name: Richard J. Minnich
Address: 1100 Superior Avenue, Suite 700
Cleveland, Ohio 44114-2518
Telephone No.: (216) 861-5582

FAY, SHARPE, BEALL, FAGAN, MINNICH & McKEE

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF ADDRESS

(check item if applicable)

10. ☐ Since the purpose of the attached documents is to record a change of address of the assignee the particulars of the previously recorded assignments for each application and/or patent are shown.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF NAME

(check item if applicable)

11. ☐ Since the purpose of the attached documents is to record a change of name of the assignee the particulars of the previously recorded assignments for each application and/or patent are shown.

CHANGE OF PATENT MAINTENANCE FEE ADDRESS

(check item if applicable)

12. ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent to the Office separately.

(Assignment (Document) Cover Sheet |16-6| --page 7 of 8)

STATEMENT (37 CFR 3.31(a)(9)) AND SIGNATURE 37 CFR 3.31(a)(10))

9

13. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Date: 6/9/93

Richard J. Minnich
(Name of party submitting document)

(Signature of party submitting document)

Richard J. Minnich
SIGNATURE OF ATTORNEY

Reg. No. 24,175

Tel. No. (216) 861-5582

Richard J. Minnich
Type or print name of Attorney

1100 Superior Avenue, Suite 700
P.O. Address

Cleveland, Ohio 44114-2518

FAY, SHARPE, BEALL, FAGAN, MINNICH & McKEE

RECEIVED 6/9/93 11:58

ASSIGNMENT (DOCUMENT) COVER SHEET [16-6]
— ADDED PAGE 1)

FURTHER APPLICATION(S) AND/OR PATENTS BEING ASSIGNED		DETAILS OF PRIOR RECORDAL (IF ANY)
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	
For:	/	
☒X Patent: 4,812,482	Issued: March 14, 1989	
Inventors: Montaro, Fernando; Calatayud, Jose; Luna, Manuel		
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☒X Patent: 3,982,002	Issued: September 21, 1976	
Inventors: Montaro, Fernando; Vila-Coro, Antonio; Calatayud, Jose		
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	
☐ In re application:	☐ International	Reel
Serial No.: 0 /	Application	Frame
Filed:	PCT /	/
For:	/	
☐ Patent:	Issued:	

ADD ADDITIONAL PAGE FOR FURTHER APPLICATION(S) AND/OR PATENT(S) BEING ASSIGNED

CLASE 7.ª

DIEZ PESETAS

AUMENTO DE CAPITAL Y MODIFICACION DE ESTATUTOS.- ELMUQUIMICA FARMACEUTICA, S.L.".--

---

NUMERO TRES MIL CIENTO CUARENTA Y NUEVE.---

EN MADRID, mi residencia, a veintinueve de Diciembre de mil novecientos noventa y dos.---

ANTE MI, MARIA DE LOS ANGELES ESCRIBANO ROMERO, Notario del Ilustre Colegio de Madrid,

----------COMPARECEN ----------

DON JUAN CARLOS DULANTO SWAYNE, nacido el 8 de Marzo de 1.942, casado, Abogado, Y -------- vecino de madrid, Velazquez 75.- D.N.I. 33.518.483 y N.I.F. letra P.----------

DON LUIS CARLOS RODRIGO MAZURE, nacido el 20 de Enero de 1.929, casado, Abogado, ------- vecino de Madrid, Velazquez 75.- D.N.I. 01175302 y N.I.F. letra W. ----------

----------INTERVIENEN ----------

a) El primero en nombre y representación de la Compañia Mercantil "ELMUQUIMICA FARMACEUTICA, S.L." N.I.F. A-28-436822, domiciliada en Arganda del Rey (Madrid) Carretera Nacional

E. Sofía Esteves Marqués
TRADUCTORA - INTÉRPRETE
Tel.: 359 77 31
Fax.: 359 45 17

BY 0981845

III, Km. 23, constituida por tiempo indefinido como Sociedad Anonima y con la denominación de "Elmuquimica, S.A." en escritura otorgada en Madrid, el 23 de Junio de 1.976, ante el Notario Don Rafael Nuñez Lagos, inscrita en el Registro Mercantil de esta Provincia, al Tomo 4.303 general, 3.515 de la sección 3ª del Libro de Sociedades, folio 127, hoja 33.793, inscripción 1ª; cambiada su denominación primitiva por la de "Elmuquimica Farmaceutica, S.A." el domicilio social y el objeto social en escritura otorgada en Madrid el dia 23 de Mayo de 1.990, ante el Notario Don Raul Gonzalez Perez y transformada en Sociedad de Responsabilidad Limitada, en escritura otorgada en Madrid, el dia 23 de Junio de 1.992, ante el Notario Don Raul Gonzalez Perez, inscrita en el Registro Mercantil de esta Provincia, al Tomo 3719, folio 61, seoción 8ª, hoja 63585, Inscripción 1ª.

Se halla legitimado para este acto en virtud de su cargo de Secretario del Consejo de

REG 6578 FRAN S98

NOTARÍA DE DON JOSE LUIS PARDO

E. Sofía Esteve Marqués
TRADUCTORA INTÉRPRETE JURADO
Fuencarral, 200 Tel: 359 77 31
28029 MADRID (España) Fax: 350 45 17

Administración de la Sociedad, cargo para el que ha sido nombrado por acuerdo del Consejo de Administración en su reunión celebrada el dia 17 de Noviembre de 1.992, y elevado a público, en escritura otorgada en Madrid, ante mi, el dia de hoy y por acuerdo adoptado por la Junta General Universal de socios de la Sociedad y el Consejo de Administración, en su reunion celebrada el dia 17 de Noviembre de 1.992, según acredita con certificación expedida el dia 22 de Diciembre de 1.992, por el propio compareciente en su concepto de Secretario con el Visto Bueno del Presidente Don Luis Carlos Rodrigo Mazure, que me entrega y dejo unida a esta matriz, dando fé yo, el Notario, de conocer las firmas y rubricas que la autorizan.----------

b) Y Don Juan Carlos Dulanto Swayne y Don Luis Carlos Rodrigo Mazure, mancomunadamente en nombre y representacion de la Compañia Mercantil "PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A." domiciliada en Madrid, Plaza

UA1819099

del Conde del Valle de Suchil 15, de duración indefinida, constituida en escritura otorgada en Madrid, el dia 4 de Junio de 1.982, ante el Notario Don Antonio Uribe Sorribes, inscrita en el Registro Mercantil de esra Provincia, al tomo, 31 general, 25 de la seccion 3ª folio 153, hoja 60.669-2, inscripción 1ª. N.I.F. A 28774461. ----------

Y adaptados sus Estatutos a la vigente Ley de Sociedades Anonimas, en escritura otorgada en Madrid, el dia 15 de Diciembre de 1.992, ante el Notario Don Agustin Sanchez Jara, estando pendiente de inscripción en el Registro Mercantil, haciendo yo, el Notario, a este respecto la oportuna advertencia, insistiendo no obstante los comparecientes en la formalización de esta escritura ----------

Se hallan legitimados para este acto, en virtud de su cargo de Consejeros de la Sociedad, cargo que me aseguran ejercen actualmente y para el que fueron nombrados, en la propia escritura de adaptación de

NOTARIA DE DON JOSE LUIS PRADO LOPEZ MADRID

M.H.L. 9.578 FRMS 590

E. Sofía Sierra Márquez
TRADUCTORA-INTERPRETE JURADO
Tel. 350 77 31
28015 MADRID (España) Fax 350 45 17

CLASE 7ª

10 PTA

estatutos. ----------

Y especialmente facultados para este acto por acuerdo de la Junta Genral Universal de Accionistas de la Sociedad, en su reunión celebrada el dia 24 de Noviembre de 1.992, según acreditan con certificación expedida el dia 22 de Diciembre de 1.992, por el Secretario del Consejo de Administración de la Sociedad Don Juan Carlos Dulanto Swayne en su concepto de Secretario del Consejo, con el Visto Bueno del Presidente Don Luis Carlos Rodrigo, que me entrega y dejo unida a esta matriz, dando fé yo, el Notario de conocer las firmas y rubricas que la autorizan. ----------

Les identifico por sus D.N.I. exhibidos y tienen, a mi juicio, según intervienen, la capacidad legal necesaria para formalizar esta escritura de AUMENTO DE CAPITAL Y MODIFICACION DE ESTATUTOS SOCIALES y al efecto ----------

---------- EXPONEN ----------

I.- "Que "PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A." es dueña en pleno dominio;

REEL 6578 FRAMES 91

BY 0981880

según manifiesta, por diversos titulos de los derechos de propiedad industrial, consistentes en patentes, solicitudes de patente y marcas que se enumeran y valoran individualmente, en la relación anexa a la certificación unida a esta matriz, de la que formara parte integrante y fundamental de la misma y que los comparecientes, en el concepto en que intervienen declaran conocer y aceptar, por un valor conjunto de SEISCIENTOS TREINTA Y NUEVE MILLONES DE PESETAS. ----------

NO ME ACREDITAN LOS TITULOS DE ADQUISICION DE LOS RESPECTIVOS DERECHOS DE PROPIEDAD INDUSTRIAL, PATENTES, SOLICITUDES Y MARCAS, referidos y enumerados en la relación unida a esta matriz, haciendo yo, el Notario, a este respecto la oportuna advertencia, INSISTIENDO NO OBSTANTE LOS COMPARECIENTES en la formalización de esta escritura. ----------

----------II.- Que el capital de la Sociedad "Elmuquimica Farmaceutica, S.L." es de sete-cientos treinta millones setecientas mil pese-

REEL 6578 FRAME 592

NOTARIA DE LOS JOSE LUIS PARDO LOPEZ MADRID

E. Sofía Fuentes Zaragoza
TRADUCTORA JURADA
Inglés
Orense 20
28020 MADRID (España)
Tel: 350 77 31
Fax: 350 45 17

X

tas representado por setecientas treinta mil setecientas participaciones sociales de mil pesetas de valor nominal cada una, numeradas correlativamente del 1 al 730.700, ambos inclusive, integramente suscrito y desembolsado.-

III.- Que la Junta General Universal Extraordinaria de Socios de la Sociedad en su reunión celebrada el dia 21 de Diciembre de 1.992 adoptó por unanimidad el acuerdo de ampliar su capital social en la suma de seiscientos treinta y nueve millones de pesetas, mediante la emisión de seiscientas treinta y nueve mil participaciones sociales de mil pesetas de valor nominal cada una de ellas, iguales a las ya exitentes, acumulables e indivisibles, numeradas correlativamente del 730.701 al 1.369.700 ambos inclusive, siendo suscrito y desembolsado integramente en la forma y proporción que consta en la certificación unida a esta matriz y que se dá aqui por reproducida a todos los efectos, para evitar su repetición.----------

0A1819100

IV.- Que ejecutando los acuerdos adoptados por dicha Junta General y deseando formalizar el negocio jurídico expresado, en la referida certificación unida a esta matriz los comparecientes en el concepto en que intervienen,----------

---------- **OTORGAN** ----------

PRIMERO:- Don Juan Carlos Dulanto Swayne, en nombre y representación de "Elmuquimica Farmaceutica, S.L." formaliza el aumento del capital social de la misma en la suma de **SEISCIENTOS TREINTA Y NUEVE MILLONES DE PESETAS** mediante la emisión y puesta en circulación de seiscientas treinta y nueve mil participaciones sociales de mil pesetas de valor nominal cada una de ellas, numeradas correlativamente del 730.701 al 1.369.700 ambos inclusive, con los mismos derechos políticos y económicos a las ya existentes.----------

SEGUNDO.- Que el aumento de capital queda suscrito y desembolsado en su totalidad, mediante la aportación de la plena titularidad y

REEL 6578 FRAME 594

NOTARIA DE DON JOSE LUIS PARDO LOPEZ MADRID

E. Sofía Fuentes
166 53/013-0
28046 MADRID (España) Fax 350 45 17

CLASE 7.ª

10 PTA DIEZ PESETAS

el dominio de la titularidad y los derechos de propiedad industrial consistentes en las patentes solicitudes de patente y marcas enumeradas y valoradas individualmente en el anexo de la certificación unida a esta matriz

TERCERO.- "Promociones Industriales y Servicios, S.A." representada en este acto por Don Luis Carlos Rodrigo Mazure y Don Juan Carlos Dulanto Swayne Dolci en pago de las participaciones que ha suscrito, aporta y transmite a la Sociedad emitente el pleno dominio y la titularidad de la titularidad y de los derechos de propiedad industrial, consistente en las patentes, solicitudes de patente y marcas que se enumeran y valoran en la relación que se acompaña a la certificación unida a esta matriz y que se dán aqui por reproducidos a todos los efectos, para evitar su repetición, por el valor asignado y que consta en la certificación unida a esta matriz en la exposición de esta escritura que es igual al valor conjunto de las acciones sus-

REG. 6578 FOLIO 595

E. Sofía Esteras Maraña
TRADUCTORA JURADA
Gran Vía, 30 Tel: 350 77 71
28013 MADRID (España) Fax: 350 45 17

BV 0981920

critas, por dicha Compañia. ----------

La Sociedad "Almuquimica Farmaceutica, S.L." representada en este acto por Don Juan Carlos Dulanto Swayne ACEPTA Y ADQUIERE la titularidad y los derechos de propiedad industrial consistentes en las patentes, solicitudes de patente y marcas referidas, por la valoración atribuida QUE EXPRESAMENTE DECLARA CONOCER Y ACEPTAR, haciendo yo, el Notario, a este respecto, la oportuna advertencia, respecto a la falta de titulación acreditada insistiendo no obstante en el otorgamiento de esta escritura. ----------

CUARTO.- Que como consecuencia del precedente aumento de capital, Don Juan Carlos Dulanto Swayne en la representación que ostentan modifica el articulo quinto de los Estatutos Sociales ,cuya nueva redacción es como sigue:----------

"ARTICULO 5º.- El capital social es de MIL TRESCIENTOS SESENTA Y NUEVE MILLONES SETECIENTAS MIL PESETAS (1.369.700.000 pesetas) y se

REEL 6578 FRAME 596

NOTARIA DE DON JOSE LUIS PASCUAL LOPEZ MADRID

encuentra integramente suscrito y desembolsado. ----------

El capital social está dividido en UN MILLON TRESCIENTAS SESENTA Y NUEVE MIL SETECIENTAS (1.369.700) participaciones sociales de MIL PESETAS de valor nominal cada una de ellas, numeradas del 1 al 1.369.700 ambos inclusive, acumulables e indivisibles que no podrá incorporarse a titulos negociales ni denominarse acciones".----------

SOLICITAN de los Señores Registradores Mercantil y de la Propiedad Industrial, practiquen las pertinentes operaciones registrales.-

Les hago las reservas y advertencias legales, en particular, a efectos fiscales, les advierto de las obligaciones y responsabilidades tributarias que les incumben y de las consecuencias de toda índole que se derivarían de la inexactitud de sus declaraciones, Ley 8/89 de 13 de Abril.----------

Leo esta escritura a los comparecientes por renuncia que hacen de su derecho a verificarla

BY 0981940

REG. 9.578 TRANS 97.

E. Sofía Tejero Márquez
TRADUCTORA INTÉRPRETE JURADO
MADRID (España)

UA1819101

por si, del que les instruyo y hallandola conforme prestan su asentimiento a lo consignado y firman.

Y yo, el Notario,

AUTORIZO

éste instrumento público, dando fe de cuanto en el asevero y consta en tres pliegos de clase septima, serie 1G numeros 6138051, 6138052, y el del presente.- Siguen las firmas de Don Juan Carlos Dulanto Swayne y Don Luis Carlos Rodrigo Mazure. Signado: Maescribano. Rubricado. Sellado.

DOCUMENTOS UNIDOS

Aplicación Arancel, Disposición Adicional Tercera, Ley 8/89 de 13 de Abril
Base de calculo: 639.000.000 y 639.000.000 pesetas
Arancel aplicable, numeros :2, 4, 5, 7 y Norma 8
Derechos Arancelarios: Quinientas cuarenta y seis mil trescientas setenta pesetas

NOTARÍA DE DON JOSÉ LUIS OPEZ PARDO MADRID

E. Sanz Estevez Margalejo
TRADUCTORA-INTERPRETE JURADO
MADRID (España)

X

ABRIL 65.7.8 FRANCES 98

representada por su Administrador Unico, D. Antonio-Fernando Montoro Jiménez, quien firma a continuación.

- ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A., titular de 619.225 participaciones sociales, que representan el 84,75% del capital social, entidad que concurre representada por su Consejero-Delegado, D. José Antonio Gómez-Monche Vives, en virtud de carta-poder que, encontrada conforme se archiva, quien firma a continuación.

Quedó así comprobada la asistencia de los tres únicos socios de la compañía, que concurren representados en la forma antes indicada, y que representan el 100% del capital social.

Asistieron tambien a la Junta D. Luis Carlos Rodrigo Mazuré y D. Carlos Rieckhof Dolci, en su condición de miembros del Consejo de Administración de la Sociedad.

Presidió la Junta D. Luis Carlos Rodrigo Mazuré, en su condición de Presidente del Consejo de Administración, actuando como Secretario el que lo es de dicho órgano, D. Juan Carlos Dulanto Swayne.

Se procedió seguidamente a discutir el Orden del Día, el cual, después de breve deliberación, fue aprobado por unanimidad, consistiendo en los puntos siguientes:

"1.- AMPLIACION DEL CAPITAL SOCIAL DE LA COMPAÑIA

2.- CONSECUENTE MODIFICACION ESTATUTARIA

3.- PROTOCOLIZACION DE ACUERDOS.

4.- REDACCION, LECTURA Y APROBACION DEL ACTA".

A continuación, la Presidenta sugirió pasar a tratar sobre los asuntos comprendidos en el mismo, adoptándose, POR UNANIMIDAD, los siguientes acuerdos:

1.- Ampliar el capital social de la compañía, cifrado actualmente en SETECIENTOS TREINTA MILLONES SETECIENTAS MIL DE PESETAS (730.700.000 Pts.) en la cuantía de SEISCIENTOS TREINTA Y NUEVE MILLONES DE PESETAS (639.000.000 Pts.), hasta situarlo en la cifra de MIL TRESCIENTOS SESENTA Y NUEVE

MILLONES SETECIENTAS MIL PESETAS (1.369.700.000 Pts.), mediante la emisión, a la par, de SEISCIENTAS TREINTA Y NUEVE MIL (639.000) nuevas participaciones sociales de MIL PESETAS (1.000 Pts.) de valor nominal cada una, iguales a las ya existentes, acumulables e indivisibles, numeradas correlativamente del al 730.701 al 1.369.700, ambos números inclusive.

El aumento habrá de llevarse a cabo mediante aportación no dineraria, concretada como se dirá más adelante.

PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A, ALIANA, S.A. y ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A., únicos socios de la compañía, renuncian expresamente a su derecho de asumir preferente y proporcionalmente las participaciones de nueva emisión, consintiendo en que el aumento de capital acordado sea asumido y desembolsado de la siguiente manera:

- PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A., representada en este acto por D. Juan Carlos Dulanto Swayne y D. Luis Carlos Rodrigo Mazuré, en su condición de Consejeros-Delegados mancomunados de la sociedad, facultados, además, expresamente por acuerdo de Junta General de la compañía, aporta la plena titularidad y el dominio de los derechos de propiedad industrial, consistente en patentes, solicitudes de patente y marcas que se enumeran y valoran individualmente, en el documento que se acompaña a la presente, formando parte integrante de la misma y que los asistentes declaran conocer y aceptar.

  La totalidad de los derechos de propiedad industrial aportados por PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A., tienen un valor neto de SEISCIENTOS TREINTA Y NUEVE MILLONES DE PESETAS (639.000.000 Pts.), importe en el que se cifra la aportación de PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A.

En consecuencia, las participaciones de nueva emisión son adjudicadas, en su condición de íntegramente desembolsadas, de la siguiente manera:

- PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A. recibe SEISCIENTAS TREINTA Y NUEVE MIL (639.000) nuevas participaciones sociales, números 730.701 al 1.369.700, ambos inclusive.

A las anteriores aportaciones les resultará de aplicación lo dispuesto en los artículos 8 y 9 de la Ley de Régimen Jurídico de las Sociedades de Responsabilidad Limitada.

2.- Como consecuencia del acuerdo anterior, modificar el artículo 5º de los Estatutos sociales, el mismo que, en lo sucesivo, tendrá la siguiente redacción:

"Artículo 5º.- El capital social es de MIL TRESCIENTOS SESENTA Y NUEVE MILLONES SETECIENTAS MIL PESETAS (1.369.700.000 Pts.), y se encuentra integramente suscrito y desembolsado.

El capital social está dividido en UN MILLOSN TRESCIENTAS SESENTA Y NUEVE MIL SETECIENTAS (1.369.700) participaciones sociales de MIL PESETAS de valor nominal cada una de ellas, numeradas del 1 al 1.369.700, ambos inclusive, acumulables e indivisibles, que no podrán incorporarse a títulos negociables ni denominarse acciones."

3.- Facultar con las más amplias atribuciones al Secretario del Consejo, D. Juan Carlos Dulanto Swayne, para que, en nombre y representación de la sociedad, comparezca ante todas las autoridades pertinentes, particularmente ante Notario, y protocolice los acuerdos adoptados por esta Junta que tengan el carácter de inscribibles, así como para que, en general, realice todos los trámites necesarios hasta ultimar la inscripción de los mismos en el Registro Mercantil, pudiendo suscribir al efecto cuantos documentos públicos y/o privados sean necesarios sin limitación alguna, incluyéndose expresamente le facultad de otorgar escrituras de subsanación, cuidando de insertar en la escritura pública de ampliación de capital todos los documentos exigidos por la Ley, aun cuando incida en la figura jurídica de autocontratación.-

4.- Redactar y dar lectura al acta de la reunión, que es aprobada por unanimidad y firmada por el Presidente y el Secretario.

CLASE 7ª

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No habiendo más asuntos que tratar, por el Presidente se levanta la sesión a las trece horas del mismo día."

EN FE DE LO CUAL EXTIENDO LA PRESENTE CERTIFICACION CON EL VISTO BUENO DEL PRESIDENTE, EN MADRID, A VEINTIDOS DE DICIEMBRE DE MIL NOVECIENTOS NOVENTA Y DOS.

Siguen dos firmas.

VºBº EL PRESIDENTE
Luis Carlos Rodrigo

EL SECRETARIO
Juan Carlos Dulanto

NOTARIA DE D. JOSE-LUIS RIAÑO LOPEZ MADRID

REEL 6578 FRAME 602

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CLASE 7.ª

PATENTES

REG. NO. 903.651
CONC: 29/11/85
PAIS: BELGICA
VALOR: 20 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

REG. NO. 2.573.071
CONC: 14/11/85
PAIS: FRANCIA
VALOR: 60 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

REG. NO. 670823
CONC:
PAIS: SUIZA
VALOR: 20 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

REG. NO. 1.184.670
CONC: 28/10/87
PAIS: ITALIA
VALOR: 50 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

NOTARIA DE MADRID

REEL 6578 FRAME 603

"CICLESONIDE"

- FRANCIA: Solicitud de Patente nº 91 10682:	11.500.000 Pts.
- ITALIA: Solicitud de Patente nº 91A002296:	8.600.000 Pts.
- REINO UNIDO: Solicitud de Patente nº 9118967.0:	10.000.000 Pts.
- R.F.A.: Solicitud de Patente nº P41295358:	14.500.000 Pts.
- GRECIA: Solicitud de Patente nº 910100353:	2.000.000 Pts.
- PORTUGAL: Solicitud de Patente nº 98897:	2.000.000 Pts.
- HOLANDA: Solicitud de Patente nº 9101472:	5.000.000 Pts.
- BELGICA: Solicitud de Patente nº 9100816:	2.800.000 Pts.
- LUXEMBURGO: Solicitud de Patente nº 88001:	700.000 Pts.
- JAPON: Solicitud de Patente nº 227418:	30.000.000 Pts.
- AUSTRALIA: Solicitud de Patente nº 8368691:	5.000.000 Pts.
- SUIZA: Solicitud de Patente nº 02619-913:	2.800.000 Pts.
- R.O.C.: Solicitud de Patente nº 15617/91:	2.000.000 Pts.
- CANADA: Solictud de Patente nº 2.050.812-4:	9.300.000 Pts.

NOTARIA DE DON JOSE LUIS [illegible] MADRID

REL 95,78 FRANCOS

X

E. Sofía Esteras Marqués
[illegible]
MADRID (España)
Fax: 350 45 17
M93/0132-0

- AUSTRIA: Solicitud de Patente nº A1769/91:	2.800.000 Pts.
- U.S.A.: Solicitud de Patente nº 578942:	47.000.000 Pts.
SUBTOTAL:	156.000.000 Pts.
"CETOVINCA"	
- BENELUX: Marca nº 334058:	500.000 Pts.
- R.F.A.: Marca nº 951540:	1.000.000 Pts.
- FRANCIA: Marca nº 920766:	2.000.000 Pts.
- ITALIA: Marca nº 321876:	1.000.000 Pts.
- SUIZA: Marca nº 279288:	500.000 Pts.
SUBTOTAL:	5.000.000 Pts.
"OXOVINCA"	
- R.F.A.: Marca nº 963183:	1.000.000 Pts.
- FRANCIA: Marca nº 924576:	2.000.000 Pts.
- ITALIA: Marca nº 321877:	1.000.000 Pts.
- SUIZA: Marca nº 279289:	500.000 Pts.
SUBTOTAL:	4.500.000 Pts.
TOTAL:	**639.000.000 PTS.**

REEL 657.8 FRAME 605

E. Sofía Esteve Margarit
Agente de la Propiedad Industrial
Fortuny, 20 Tel. 319 77 91
28010 MADRID (España) Fax: 319 45 17

B93/013-0

1

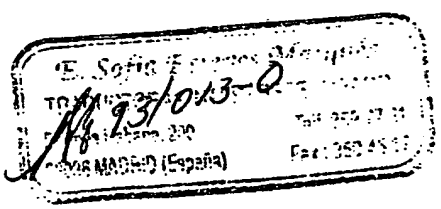
RELACION DE PATENTES, SOLICITUDES DE PATENTE Y MARCAS APORTADAS POR "PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A." Y VALORACION DE LAS MISMAS

"FEPRADINOL, HCI"

- BELGICA: Patente nº 903.651:	20.000.000 Pts.
- FRANCIA: Patente nº 2.573.071:	60.000.000 Pts.
- SUIZA: Patente nº 670.823:	20.000.000 Pts.
- ITALIA: Patente nº 1.184.670:	50.000.000 Pts.
- U.S.A.: Patente nº 4.812.482:	147.000.000 Pts.
- PORTUGAL: Patente nº 81.479:	10.000.000 Pts.
- JAPON: Solicitud de Patente nº 60-249.089:	90.000.000 Pts.
SUBTOTAL:	397.000.000 Pts.

"2 VINCAMINE CETOGLUTARATE"

- U.S.A.: Patente nº 3982002:	28.000.000 Pts.
- BELGICA: Patente nº 823806:	5.000.000 Pts.
- R.F.A.: Patente nº P-2500599-6-09:	9.000.000 Pts.
- LUXEMBURGO: Patente nº 71545:	1.500.000 Pts.
- SUIZA: Patente nº 593974:	4.000.000 Pts.
- FRANCIA: Patente nº 7430299 (2283669):	15.000.000 Pts.
- JAPON: Patente nº 1093823:	14.000.000 Pts.
SUBTOTAL:	76.500.000 Pts.



REG. NO. 4.812.482
CONC: 14/03/89
PAIS: U.S.A.
VALOR: 147 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

REG. NO. 81.479
CONC: 07/04/87
PAIS: PORTUGAL
VALOR: 10 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

REG. NO. 60.249.089
CONC:
PAIS: JAPON
VALOR: 90 MILLONES DE PTS.

α[[(2-hidroxy-1,1-diaméthyl-éthyl)amino]méthyl], benceno methanol y sus sales, sus procedimientos de preparación y utilización.

REG. NO. 3982002
CONC: 21/09/76
PAIS: U.S.A.
VALOR: 28 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REEL 6578 FRAME 608

REG. NO. 823806
CONC: 14/01/75
PAIS: BELGICA
VALOR: 5 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REG. NO. P-2500599-6-09
CONC: 09/01/75
PAIS: ALEMANIA
VALOR: 9 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REG. NO. 71545
CONC: 17/06/75
PAIS: LUXEMBURGO
VALOR: 1,5 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REG. NO. 593974
CONC: 31/08/77
PAIS: SUIZA
VALOR: 4 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REG. NO. 7430299 (2283669)
CONC: 21/07/78
PAIS: FRANCIA
VALOR: 15 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REG. NO. 1093823
CONC:
PAIS: JAPON
VALOR: 14 MILLONES DE PTS.

Procedimiento de preparación de 2-cetoglutarato de vincamina. Sustancia que actúa como vaso dilatador.

REG. NO. 91 10682
SOL.: 07/09/90
PAIS: FRANCIA
VALOR: 11,5 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 91A002296
SOL.: 07/09/90
PAIS: ITALIA
VALOR: 8,6 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 9118967.0
SOL.: 03/09/91
PAIS: REINO UNIDO
VALOR: 10 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. P41295358
SOL.: 05/09/91
PAIS: ALEMANIA
VALOR: 14,5 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 910100353
SOL.: 13/08/91
PAIS: GRECIA
VALOR: 2 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 98897
SOL.: 09/06/91
PAIS: PORTUGAL
VALOR: 2 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 9101472
SOL.: 30/08/91
PAIS: PAISES BAJOS
VALOR: 5 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 9100816
SOL.: 02/09/91
PAIS: BELGICA
VALOR: 2,8 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 88001
SOL.: 04/09/91
PAIS: LUXEMBURGO
VALOR: 0,7 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 227418
SOL.: 06/09/91
PAIS: JAPON
VALOR: 30 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 8368691
SOL.: 06/09/91
PAIS: AUSTRALIA
VALOR: 5 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 02619-913
SOL.: 06/09/91
PAIS: SUIZA
VALOR: 2,8 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 15617/91
SOL.: 07/09/91
PAIS: COREA
VALOR: 2 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. 2050812-4
SOL.: 06/09/91
PAIS: CANADA
VALOR: 9,3 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REG. NO. A1769/91
SOL.: 06/09/91
PAIS: AUSTRIA
VALOR: 2,8 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

REEL 657 FRAME 612

OA1819105

REG. NO. 578942
SOL.: 28/08/91
PAIS: U.S.A.
VALOR: 47 MILLONES DE PTS.

Procedimiento de preparación de nuevos esteroides de pregna-1,4-dieno-3,20-diona-16-17-acetal-21 y sus métodos para el tratamiento de estados inflamatorios.

BY 0981058

CLASE 7.ª

0A1819106

MARCAS

MARCA	CLASE	NO. REG.	CONC.	PAIS	VALOR (*)
CETOVINCA	5	334058	30/03/76	BENELUX	0,5
CETOVINCA	5	951540	22/11/76	ALEMANIA	1
CETOVINCA	5	920766	28/03/75	FRANCIA	2
CETOVINCA	5	321876	22/04/80	ITALIA	1
CETOVINCA	5	279288	17/12/75	SUIZA.	0,5
OXIVINCA	5	963183	28/09/77	ALEMANIA	1
OXOVINCA	5	924576	28/03/75	FRANCIA	2
OXOVINCA	5	321877	22/04/80	ITALIA	1
OXOVINCA	5	279289	17/12/75	SUIZA	0,5

(*) MILLONES DE PESETAS

D. JUAN CARLOS DULANTO SWAYNE
SECRETARIO DEL CONSEJO DE ADMINISTRACION DE
"PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A."

C E R T I F I C O:

Que en la Junta General Extraordinaria de Accionistas de la sociedad que represento, celebrada con carácter universal, el día 18 de Diciembre de 1992, con la asistencia de la totalidad de los accionistas luego de que aceptaran por unanimidad la celebración de la Junta y los asuntos a tratar, se adoptaron, también por unanimidad, los acuerdos que constan en el acta a que dio lugar dicha reunión y que a continuación se transcribe literalmente en su integridad:

"En Madrid, siendo las nueve horas del día 18 de Diciembre de 1992, se reune en el domicilio social, sito en la Plaza del Conde del Valle de Suchil, 15 la Junta General Extraordinaria de la sociedad, estando presente la totalidad de los accionistas que representan la totalidad del capital social.

Los asistentes aceptan por unanimidad constituirse en Junta General Extraordinaria con el carácter de Universal, sin el requisito de convocatoria previa, conforme a lo dispuesto en el artículo 99 del Texto Refundido de la Ley de Sociedades Anónimas, aprobado por Real Decreto Legislativo 1564/89 de 22 de Diciembre.

Formada la lista de asistencia con arreglo a lo previsto en el artículo 111 del Texto Refundido de la Ley de Sociedades Anónimas y Articulo 98 del Reglamento del Registro Mercantil, se comprueba la concurrencia de todos los accionistas de la sociedad, titulares de la totalidad de las acciones:

- SERVICIO IBERICO DE CONSULTORES, S.A., titular de 9.000 acciones, que representan el 75% del capital social, representada en este acto por D. Juan Carlos Dulanto Swayne, en virtud de carta poder que, encontrada conforme se archiva, quien concurre igualmente en su condición de Secretario-Consejero de la sociedad y firma a continuación.

BY 0981078

- D. Juan Carlos Dulante Swayne, titular de 1.500 acciones, que representan el 12,5% del capital social, quien concurre igualmente en su condición de Consejero de la sociedad y firma a continuación.

- D. Luis Carlos Rodrigo Mazuré, titular de 1.500 acciones, que representan el 12,5% del capital social, quien concurre igualmente en su condición de Consejero y Presidente de la sociedad y firma a continuación.

Con la concurrencia de los tres citados accionistas, que asisten personalmente en la forma antes indicada, se comprueba la presencia de la totalidad de los accionistas de la sociedad, que representan la totalidad del capital social.

A los efectos del articulo 104.2 del Texto Refundido de la Ley de Sociedades Anónimas, se hace constar expresamente que asisten igualmente, en su condición de miembro del Consejo de Administración de la sociedad, D. Carlos Rieckhof Dolci.

De conformidad con lo dispuesto en el articulo 110 del Texto Refundido de la Ley de Sociedades Anónimas, actúa como Presidente de la Junta, D. Luis Carlos Rodrigo Mazuré, y como Secretario D. Juan Carlos Dulanto Swayne, quienes ocupan dichos cargos en el seno del Consejo de Administración.

Se procede seguidamente a discutir acerca del Orden del Día, resultando aprobado el siguiente:

"ORDEN DEL DIA

1. AUTORIZACION PARA CONCURRIR A LA AMPLIACION DE CAPITAL DE LA SOCIEDAD "ELMUQUIMICA FARMACEUTICA, S.L."

2. REDACCION, LECTURA Y, EN SU CASO, APROBACION DEL ACTA DE LA REUNION"

El Presidente manifiesta estar válidamente constituída en primera convocatoria la Junta con quórum y con capacidad suficientes para tratar sobre los asuntos comprendidos en el Orden del Día de la convocatoria, sin que se formule por los asistentes reservas o protestas respecto de las anteriores manifestaciones del Presidente.

NOTARIA DE DON JOSE-LUIS PRADOS PRADA MADRID

A continuación, el señor Presidente sugiere pasar a tratar sobre los asuntos comprendidos en el Orden del Día, adoptándose POR UNANIMIDAD, con el voto favorable de la totalidad de las acciones que componen el capital social, los siguientes acuerdos:

PRIMERO: Facultar expresamente a los tres miembros del Consejo de Administración de la compañía, los Sres. D. Luis Carlos Rodrigo Mazuré, D. Juan Carlos Dulanto Swayne y D. Carlos Rieckhof Dolci para que, actuando mancomunadamente, dos cualesquiera de ellos, puedan concurrir a la ampliación de capital que tendrá lugar, en fecha 21 de Diciembre de 1992, en la sociedad "ELMUQUIMICA FARMACEUTICA, S.L.", mediante aportación no dineraria, consistente en la aportación de patentes, solicitudes de patente y marcas propiedad de la sociedad, aún cuando en los actos para los que se les faculta pueda darse la figura jurídica de auto-contratación.

SEGUNDO: Aprobar, en este mismo acto, el acta de la reunión que se está llevando a cabo, la cual es redactada y leida por el señor Secretario, siendo firmada a continuación por el Presidente y el Secretario.

Y no habiendo más asuntos que tratar, se levanta la sesión por el Sr. Presidente siendo las diez horas."

Y, EN FE DE LO CUAL, EXTIENDO LA PRESENTE CERTIFICACION EN MADRID, A 22 DE DICIEMBRE DE 1992

Siguen dos firmas.----------

EL PRESIDENTE
Luis Carlos Rodrigo

EL SECRETARIO
Juan Carlos Dulanto

ES PRIMERA COPIA EXACTA E INTEGRA DE SU MATRIZ, donde anoto esta saca, que expido a instancia de "ELMUQUIMICA FARMACEUTICA, S.L.", en ocho pliegos de clase septima, serie OA, números 1.819.099 y los siete siguientes en orden correlativo, en Madrid, el dia de su otorgamiento.- DOY FE.-

E. Sofía Esteras Marqués
Fax: 350 45 17

REEL 6578 FRAME 617

BY 0981098

PAPEL EXCLUSIVO PARA DOCUMENTOS NOTARIALES

1B2364373

CLASE 8ª

5 PTA

N.º 01

SECCION DE RECEPCION DE DOCUMENTOS

Con fecha 29-01-93 el interesado aporta justificantes de pago, abonará num. 228 registro de Caja n.º 108 de la liquidación número ____ por el Impuesto de Transmisiones Patrimoniales. Por un importe de 6.390.000 ptas.

Todo ello sin perjuicio de la verificación del citado justificante de pago.

Madrid, 29-01-93

El Jefe de la Sección

MARIA DE LOS ANGELES ESCRIBANO ROMERO, Notario del Ilustre Colegio de Madrid, con residencia en la capital:

Doy fé: Que la presente xerocopia compuesta de 17 folios, concuerda con su original que me ha sido exhibido a efectos de cotejo e identificación.

Madrid, - 9 FEB. 1993

DOCUMENTO SIN CUANTIA LEY 8/89 DE 13 DE ABRIL

E. Sofía Fuentes Mercadé
TRADUCTORA-INTÉRPRETE JURADO
Inglés - Francés
MADRID (España)
Tel. 350 77 31
Fax: 350 45 17

93/013

REEL 6578 FRAME 618

ILUSTRE COLEGIO NOTARIAL DE MADRID

DECANATO

Legalización del signo, firma y rúbrica de
DON MARIA DE LOS BUENOS CERVIDAS ROMERO
Notario de este Ilustre Colegio.
Madrid, a CINCO de MARZO
de mil novecientos noventa y tres

D José María Lucena Conde
Miembro de la Junta Directiva en funciones de Decano

SELLO DE LEGALIZACIONES
CINCO PESETAS

LEGALIZACION.-Visto en esta Dirección general de Registros y del Notariado para legalizar la firma de
D. José María Lucena Conde
Decano del Colegio Notarial de Madrid
Madrid 10 de Marzo de 1993
P. El Director General

DIRECCION GRAL. DE LOS REGISTROS Y DEL NOTARIADO Ministerio de Justicia

Angel Marcio García
JEFE DE LA SECCION DEL NOTARIADO

MINISTERIO DE ASUNTOS EXTERIORES
LEGALIZACIONES
Madrid 11 MAR. 1993
Visto bueno para legalizar la firma que antecede por ser, el parecer auténtica.
P. El Subsecretario.

ALICIA LOPEZ ALGUACIL
Jefe Auxiliar de Legalizaciones

5853

10 MAR 1993

Mª Teresa Izquierdo Meyniel

REF. 6578 FRANCO 19

BY 098111

El presente folio de papel agregado al documento en el que figura la firma de
D. /Dª María de los Angeles Echaniz Ribero
fecha 7 Febrero 1997

Apostille (o legalización única)
(Convention de La Haye du 5 octobre 1961)
(Real Decreto 2433/1978, de 2 de octubre)

1. **País:** *España*
   El presente documento público
2. **Ha sido firmado por** Dña. María de los Angeles Echaniz Ribero
3. **Actuando en calidad de** *NOTARIO*
4. **Se halla sellado/timbrado con** *el de su Notaría*

CERTIFICADO

5. **En Madrid** 6. **El** 12 Marzo 1997
7. **Por el Decano del Colegio Notarial de Madrid**
8. **Con el número** 46137
9. **Sello/timbre:** 10. **Firma:**

D. José María Lucena Conde
Miembro de la Junta Directiva en funciones de Decano

SELLO DE LEGALIZACIONES — CINCO PESETAS

REEL 6578 FRAME 620

BY 0955956

MODELO

ADMINISTRACION DE: MADRID — Código Administración: 28600

OFICINA LIQUIDADORA

Espacio reservado para la etiqueta identificativa

TU5133 25 ENE 1993

600201048200 2

DIA 29 MES 12 AÑO 92

(4) NUMERO DE SUJETOS PASIVOS: 0 1

(6) TRANSMITENTE

N.I.F.: B-28.436.822

APELLIDOS Y NOMBRE O RAZON SOCIAL: [illegible] PRODUCCIONES Y A.I.D. FITOQUIMICA FARMACEUTICA, S.L.

VIA PUBLICA: CARRETERA NACIONAL III, KM. 23

NUMERO | ESC. | PISO | PRTA. | TELEFONO

MUNICIPIO: ARGANDA DEL REY

PROVINCIA: MADRID

CODIGO POSTAL: 28500

N.I.F. | APELLIDOS Y NOMBRE O RAZON SOCIAL

VIA PUBLICA Y NUMERO | MUNICIPIO | PROVINCIA | (5) Nº DE TRANSMITENTES | CODIGO POSTAL

(7) PUBLICO P / PRIVADO B

(8) EXPRESION ABREVIADA

(9) CONCEPTO: OPERACION SOCIETARIA

(10) NOTARIO O FEDATARIO: MARIA DE LOS ANGELES ESCRIBANO ROMERO

(11) Nº PROTOCOLO: 3149

(12) IDENTIFICACION DEL BIEN OPERACION O ACTO: AMPLIACION DE CAPITAL

(13) MUNICIPIO | PROVINCIA | CODIGO POSTAL

(14) DECLARACION DEL BIEN OPERACION O ACTO

(15) VALOR DECLARADO

Exentos E ☐ No sujetos N ☐

(16) FUNDAMENTO DEL BENEFICIO FISCAL O NO SUJECION

(17) ☐ LIQUIDACION COMPLEMENTARIA

- Nº PRIMERA LIQUIDACION

- FECHA PRESENTACION

Base Imponible		1	639.000.000
Reducción	2 %	3	--------
Base liquidable	1 - 3 =	4	639.000.000
Tipo		5	1 %
Cuota		6	6.390.000
Bonificación cuota	7 %	8	--------
Ingresar	6 - 8 =	9	6.390.000
		10	
		11	
TOTAL A INGRESAR		12	6.390.000

N.I.F.: A-28774461

APELLIDOS Y NOMBRE O RAZON SOCIAL: PROMOCIONES INDUSTRIALES Y SERVICIOS SA

VIA PUBLICA: C/ CONDE VALLE SUCHIL | NUMERO: 15 | ESC. | PISO | PRTA. | MUNICIPIO: MADRID | TELEFONO | CODIGO POSTAL: 28020 | PROVINCIA: MADRID

El sujeto pasivo o presentador del documento declara bajo su responsabilidad que, junto con el documento original, presenta una copia simple que coincide en todos sus términos con los de aquél.

Madrid 29 de Enero de 1993

FIRMA DEL SUJETO PASIVO O PRESENTADOR DEL DOCUMENTO

Sello: 28600 2689329332

Fecha: 29/01/1993

Número: 6.390.000 Pese

Importe: 223 ,00

30 € (Impreso por el Colegio de Registradores de la Propiedad)

BY 0981138

FE DE IDENTIDAD

Yo, MARIA DE LOS [illegible] ESCRIBANO ROMERO, Notario del Ilustre Colegio de Madrid con residencia en la Capital,

DOY FE: De que la presente copia coteja punto a punto fielmente con el original que reproduce, el cual me ha sido exhibido para su cotejo e identificación.

Madrid, a 15 FEB. 1993

DOCUMENTO SIN CUANTIA LEY 8/89 DE 13 DE ABRIL

NOTARIA DE DON JOSE LUIS PIÑEL LOPEZ MADRID

REFL 6578 FRAM 622

Sofía Esteves Marqués
TRADUCTORA - INTERPRETE JURADO
[illegible], 220 Tel: 359 77 31
MADRID (España) Fax: 350 45 17

5.853

Yo, **E. Sofía Esteves Marqués,** *Intérprete Jurado del Idioma Inglés por nombramiento del Ministerio de Asuntos Exteriores del Estado Español, y miembro activo de la Asociación Americana de Traductores y de la Asociación Nacional de Traductores e Intérpretes Judiciales de los Estados Unidos,*

Certifico:

Que las hojas del presente documento, que llevan mi sello, media firma y el número 93/013-O de mi protocolo, son traducción fiel, a mi leal saber y entender, de dichas hojas del Documento Original adjunto, del mismo número, sello y media firma.

Y para que así conste, firmo y pongo mi sello en Madrid, a 23 de febrero de 1993.

* * *

I, **E. Sofía Esteves Marqués,** *Certified Translator of the English Language by appointment of the Spanish Ministry of Foreign Affairs and Active Member of the American Translators Association and the National Association of Judiciary Interpreters and Translators of the United States,*

Certify:

That the pages of this document, bearing my seal, initials and the number 92/008-O of my Record, are a true and faithful translation, to the best of my ability, of the attached pages of this Original Document, bearing the same number, seal and initials.

In testimony whereof, I set my hand and seal in Madrid, on February 23th, 1993.

NOTARÍA DE DON JOSÉ LUIS PRADO LOPEZ

REEL 6578 FRAME 623

INCREASE IN CAPITAL AND MODIFICATION OF THE BY LAWS

"ELMUQUIMICA FARMACEUTICA, S.L."

NUMBER THREE THOUSAND ONE HUNDRED AND FORTY NINE.

IN MADRID, in my residence on the twenty-ninth day of December, nineteen hundred and ninety two.----------

BEFORE ME, MARIA DE LOS ANGELES ESCRIBANO ROMERO, Notary member of the Madrid Notarial Association----------

----------APPEAR----------

Mr. Juan Carlos DULANTO SWAYNE, born on the 8th of March, 1942, married, Attorney and resident in Madrid, at 75 Velazquez St., bearing National Identity Document #33.518.483 and Fiscal Identification Code letter P.----------

Mr. Luis Carlos RODRIGO MAZURE, born on the 20th of January, 1929, married, Attorney and resident of Madrid, at 75 Velazquez St., bearing National Identity Document #01175302 and Fiscal Identification Code letter W.----------

----------THEY APPEAR----------

a) The first one on behalf of and representing the Business Company "ELMUQUIMICA FARMACEUTICA, S.L.", bearing Fiscal Identification Number A/28-436822, with registered offices in Arganda del Rey (Madrid), National Road III, Km. 23, established for an

REEL 6578 FRAME 624

E. Sofía Esteras Olmedilla
TRADUCTORA-INTÉRPRETE JURADO
Nº 93/03
MADRID (España)
Tel: 359 77 91
Fax: 350 45 17

BY 0981181

indefinite period of time as a corporation under the name "Elmuquimica, S.A.", in public instrument executed in Madrid, on the 23rd of June, 1976, before the Notary Public Mr. Rafael NUÑEZ LAGOS, registered in the Government Register of Commercial Concerns of this Province, in General Volume 4.303, 3.515 of the Third Section of the Book of Companies, folio 127, page 33.793, first entry; changing its original name for that of "Elmuquimica Farmaceutica, S.A., the registered offices and the corporate object in public document executed in Madrid on the 23rd day of May, 1990, before the Notary Public Mr. Raul GONZALEZ PEREZ, and transformed into a Limited Liability Company through public instrument executed in Madrid on the 23rd day of June, 1992, before the Notary Public Mr. Raul GONZALEZ PEREZ, registered in the Government Register of Commercial Concerns of this Province in volume 3719, folio 61, 8th section, page 63585, First entry.----------

He is empowered for this act by virtue of his office as Secretary of the Board of Directors of the Company, position to which he was appointed by resolution of the Board of Directors passed in its Meeting held on November 17th. 1992, and public instrument executed in Madrid before me today, and by resolution passed by the General Universal Meeting of Shareholders of the Company and the Board of Directors, in its Meeting held on November 17th, 1992, as accredited through certification issued on December 22nd, 1992 by the appearing party himself, as Secretary, with the approval of the President Mr. Luis Carlos RODRIGO MAZURE, which he delivers to me and which will remain attached to this original, and I the Notary certify that I am acquainted with the signatures and personal marks authorizing such.-

NOTARIA DE DON JOSE-LUIS PARDO LOPEZ MADRID

REEL 6578 FRAME 625

E. Sofía Esteves Marqués
TRADUCTORA JURADA
MADRID (España)
Fax: 350 45 17

M-53/013-0

b) And Mr. Juan Carlos DULANTO SWAYNE and Mr. Luis Carlos RODRIGO MAZURE, jointly on behalf of and representing the Business Company "PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A.", with registered offices in Madrid, at #15 Plaza del Conde del Valle de Suchil, established for an indefinite period of time through public instrument executed in Madrid on the 14th day of June, 1982, before the Notary Public Mr. Antonio URIBE SORRIBES, registered in the Government Register of Commercial Concerns of this Province, in general volume 31, number 25 of the Third Section, folio 153, page 60.669-2, First entry. Fiscal Identification Code A 28/774461.------

And having adapted its By Laws to the Companies Act in force though public instrument executed in Madrid, on December 15th, 1992, before the Notary Public Mr. Agustin SANCHEZ JARA, pending registration in the Government Register of Commercial Concerns, and I the Notary, issuing at this time the corresponding warning, the appearing parties nevertheless insist on executing this public instrument.----------

They are empowered for this act by virtue of their office as Members of the Board of Directors, office which they assure me they presently hold and for which they were appointed in the same public instrument of adaptation of the By Laws.----------

And they are specially empowered for this act by resolution of the General Universal Meeting of Shareholders of the Company, in its Meeting held on November 24th, 1992, as accredited through certification issued on December 22nd, 1992 by the Secretary of the Board of Directors of the Company Mr. Juan Carlos DULANTO SWAYNE as Secretary of the Board, with the Approval of the President Mr. Luis

BY 0981206

Carlos RODRIGO, which is delivered to me and which I leave attached to this original, and I the Notary certify that I am acquainted with the signatures and personal marks authorizing such.----------

I identify them through their National Identity Documents which they show me, and they have, in my opinion, as they appear, the necessary legal capacity to execute this Public Instrument for the INCREASE IN CAPITAL AND MODIFICATION OF CORPORATE BY LAWS, and to such an end----------

----------SET FORTH----------

I. That "PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A." holds absolute ownership as set forth through several titles, to the industrial property rights, consisting of patents and trademarks which are listed and assessed individually in the list attached to the certification attached to this original, and of which it will form integral and fundamental part, and that the appearing parties, as they appear, declare that they know and accept such for a total sum of SIX HUNDRED AND THIRTY NINE MILLION PESETAS.----------

THE PURCHASE TITLES OF THE RESPECTIVE INDUSTRIAL PROPERTY RIGHTS, PATENTS, APPLICATIONS AND TRADEMARKS ARE NOT ACCREDITED TO ME, identified and enumerated in the list attached to this original, and I the Notary, issuing to this respect, the adequate warning, THE APPEARING PARTIES NEVERTHELESS INSIST on the execution of this public instrument.----------

II.- That the capital of the Company "Elmuquimica Farmaceutica, S.L." is seven hundred and thirty million seven hundred thousand

pesetas represented by seven hundred and thirty thousand seven hundred company shares with a nominal value of one thousand pesetas each, numbered correlatively from 1 through 730,700, completely subscribed and disbursed.----------

III.- That the General Universal Extraordinary Meeting of Shareholders of the Company in its Meeting held on December 21st, 1992, unanimously passed a resolution to increase it corporate capital in the sum of six hundred and thirty nine million pesetas, by issuing six hundred and thirty nine thousand corporate shares with a nominal value of one thousand pesetas each, equal to the existing ones, accumulative and indivisible, numbered correlatively from 730,701 through 1,369,700, completely subscribed an disbursed in the manner and proportion set forth in the certification attached to this original and which is deemed as reproduced here to all effects, so as to avoid repetition.----------

IV.- That in carrying out the resolutions passed by said General Meeting of Shareholders and wishing to execute the legal transaction set forth in the aforementioned certification attached to this original, the appearing parties, as they appear----------

----------EXECUTE----------

FIRST. Mr. Juan Carlos DULANTO SWAYNE, on behalf and representing "Elmuquimica Farmaceutica, S.L." formalizes the increase of corporate capital of same in the sum of SIX HUNDRED AND THIRTY NINE MILLION PESETAS, through the issuance and circulation of six hundred and thirty nine thousand corporate shares with a nominal

value of one thousand pesetas each, numbered correlatively from 730,701 through 1,369,700, with the same political and economic rights as the existing ones.----------

SECOND. That the increase in capital is totally subscribed and disbursed by evidencing absolute ownership and fee simple and the rights of industrial property consisting on the patents, application for patents and trademarks listed and valued individually in the annex to the certification attached to this original.----------

THIRD. "Promociones Industriales y Servicios S.A." represented in this act by Mr. Luis Carlos RODRIGO MAZURE and Mr. Juan Carlos DULANTO SWAYNE DOLCI in payment for the shares subscribed presents and transfers to the issuing Company absolute ownership and fee simple of the industrial property rights, consisting of patents, application for patents and trademarks listed and assessed in the list accompanying the certification attached to this original and which are deemed to be reproduced to all effects so as to avoid repetition, for the value assigned, which appears in the certification attached to this original in the statement, and which is equal to the total value of the shares subscribed by said Company.----------

The Company "Almuquimica Farmaceutica S.L." *(sic)*, represented in this act by Mr. Juan Carlos DULANTO SWAYNE, ACCEPTS AND ACQUIRES the ownership and industrial property rights consisting on the patents, application for patents and trademarks mentioned above for the value they are granted WHICH IT EXPRESSLY DECLARES TO KNOW AND TO ACCEPT, issuing I the Notary in this respect, the corresponding warning regarding the lack of accredited ownership, it nevertheless insisting on the execution of this public

NOTARÍA DE DON JOSÉ-LUIS PALOMO LÓPEZ MADRID

REEL 6578 FRAME 629

E. Sofía Esteves Mendiola
TRADUCTORA - INTÉRPRETE JURADA
M-53013-0

instrument.----------

FOURTH. That as consequence of the preceding increase in capital, Mr. Juan Carlos DULANTO SWAYNE with the powers he holds, modifies Article Five of the Corporate By Laws, which shall from now on read as follows:----------

"ARTICLE 5. - The corporate capital is PESETAS ONE THOUSAND THREE HUNDRED AND SIXTY NINE MILLION SEVEN HUNDRED THOUSAND (Pesetas 1,369,700,000), and is completely subscribed and disbursed.----------

The corporate capital is divided into ONE MILLION THREE HUNDRED AND SIXTY NINE THOUSAND SEVEN HUNDRED (1,369,700) corporate shares with a NOMINAL VALUE OF ONE THOUSAND PESETAS each, numbered correlatively from 1 through 1,369,700, accumulative and indivisible, which cannot be incorporated to negotiable instruments nor be called stock".----------

THEY REQUEST of the Gentlemen Registrars of the Government Register of Commercial Concerns and the Industrial Property Register to carry out the corresponding registration operations.----------

I issue the corresponding reserves and legal warnings, particularly those of a fiscal nature, and warn them of their tax obligations and responsibilities and of the consequences of all types arising from inaccuracy in their declarations. Act 8/89 dated April 13th.----------

I read this public instrument to the appearing parties as they waive their right to verify it themselves, which I tell them they have, and agreeing to it, they consent to that set forth and sign.-----

I the Notary---------- ----------

----------AUTHORIZE----------

this public instrument, certifying all which I assert in such and which is comprised of three sheets of seventh class paper, Series 1G numbers 6138051, 6138052, and the present one. Below appear the signatures of Mr. Juan Carlos DULANTO SWAYNE and Mr. Luis Carlos RODRIGO MAZURE. Signed, Meascribano. Personal mark. Seal.---------

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----------ENCLOSED DOCUMENTS----------

Marginal Note:

Duty Applied, Additional Resolution Third, Act 8/89 dated April 13th.
Estimation Base: Pesetas 693,000,000 and 693,000,000.
Applicable Duty, numbers: 2,4,5,7, and Regulation 8.
Legal fees: Pesetas Five hundred and forty six thousand three hundred and seventy.

MR. JUAN CARLOS DULANTO SWAYNE,
Secretary of the Board of Directors of
ELMUQUIMICA FARMACEUTICA, S.L.

C E R T I F I E S:

That in the General Extraordinary Meeting of Shareholders of ELMUQUIMICA FARMACEUTICA, S.L., held as Universal in character on December 21st, 1992, with the attendance of all the shareholders, who unanimously accepted to hold the Meeting and the Agenda for the Day, the resolutions set forth in the Minutes of said Meeting were unanimously passed, and are transcribed literally below:

"In Madrid, at eight hours on the 21st day of December, 1992, the General Extraordinary Meeting of "ELMUQUIMICA FARMACEUTICA, S.L., Universal in character comes to order at the Registered Offices of the Company, with the attendance of all the shareholders, representing all the corporate capital.

Those present unanimously agree to meet as General Extraordinary Meeting, Universal in character, without the requirement of advance notice, in agreement with that set forth in Article 15 of the Text of the Limited Liability Companies Act.

Having drawn up the attendance list, attendance of all the shareholders of the Company is verified, owners of 100% of the corporate capital:

- PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A., owner of 16,500 Corporate shares, which represent 2.25% of the corporate capital, entity represented in this act by the Member of its Board of Directors Mr. Juan Carlos DULANTO SWAYNE, by virtue of a letter of empowerment which, being found in agreement, is filed, and who signs below.

BY 0981261

- ALIANA, S.A., owner of 94,975 corporate shares, numbered 16,001 through 20,000, representing 13% of the corporate capital, entity which equally attends represented by its Sole Administrator, Mr. Antonio - Fernando MONTORO JIMENEZ, who signs below.

- ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A., owner of 619,225 corporate shares representing 84.75% of the corporate capital, who attends represented by its Managing Director Mr. Jose Antonio GOMEZ-MONCHE VIVES, by virtue of a letter of empowerment which, being found in agreement, is filed, and who signs below.

Thus is verified the attendance of the only three shareholders, who attend, represented in the manner indicated above, and who represent 100% of the corporate capital.

Also present at this Meeting were Mr. Luis Carlos RODRIGO MAZURE and Mr. Carlos RIECKHOF DOLCI, as members of the Board of Directors of the Company.

Acting as Chairman of the Meeting was Mr. Luis Carlos RODRIGO MAZURE as President of the Board of Directors, and acting as Secretary was the Secretary of that same Body, Mr. Juan Carlos DULANTO SWAYNE.

Next the Meeting proceeded to discuss the Agenda for the Day, which after a brief discussion, was unanimously approved, consisting in the following points:

"1. TO INCREASE THE CAPITAL OF THE COMPANY

2. TO CONSEQUENTLY MODIFY THE BY LAWS

3. TO OFFICIALLY RECORD THE RESOLUTIONS

4. TO DRAW UP, READ AND APPROVE THE MINUTES".

Then the Chairman suggested dealing with the business included in the Agenda for the Day. UNANIMOUSLY passing, the following resolutions:

FIRST: To increase the corporate capital of the Company, presently set at PESETAS SEVEN HUNDRED AND THIRTY MILLION SEVEN HUNDRED THOUSAND (Ptas. 730,700,000.) in the amount of PESETAS SIX HUNDRED AND THIRTY NINE MILLION (Ptas. 639,000,000.), to reach the sum of PESETAS ONE THOUSAND, THREE HUNDRED AND SIXTY NINE MILLION SEVEN HUNDRED THOUSAND PESETAS (Ptas. 1,369,7000.-) by issuing at par value, SIX HUNDRED AND THIRTY NINE THOUSAND (639,000.-) new corporate shares of ONE THOUSAND (Ptas. 1,000.) nominal value each, equal to the already existing ones, accumulative and indivisible, numbered correlatively from 730,701 through 1,369,700.

The increase will be carried out by non-monetary contribution, as specified below.

PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A., ALIANA, S.A., and ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A., the only shareholders of the Company, expressly waive their preferential and proportional rights to the newly issued shares, consenting that the increase in capital agreed upon be taken up and disbursed in the following manner:

- PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A., represented in this Act by Mr. Juan Carlos DULANTO SWAYNE and Mr. Luis Carlos RODRIGO MAZURE, as joint Managing Directors of the Company, also empowered, by express Resolution of the General Meeting of the Company, present absolute ownership and fee simple of the rights to industrial property, consisting in patents, applications for patents, and trademarks listed and assessed individually in the document accompanying the present one, forming an integral part of same and which the persons present declare to know and accept.

All the rights to industrial property presented by PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A.m have a net value of PESETAS SIX HUNDRED AND THIRTY NINE MILLION (Ptas. 639,000,000.-), sum which comprises the contribution of PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A.

Consequently, the new shares issued are allotted, as completely disbursed, in the following manner:

- PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A. receives SIX HUNDRED AND THIRTY NINE THOUSAND (639,000) new corporate shares, numbers 730,701 through 1,369,700.

To the above contributions, that set forth in Articles 8 and 9 of the Limited Liabilities Companies Act is applicable.

2.- As consequence of the above resolution, to modify Article 5 of the Corporate By Laws, which from now on will read as follows:

"ARTICLE 5. - The corporate capital is PESETAS ONE THOUSAND THREE HUNDRED AND SIXTY NINE MILLION SEVEN HUNDRED THOUSAND (Pesetas 1,369,700,000) and is completely subscribed and disbursed.

The corporate capital is divided into ONE MILLION THREE HUNDRED AND SIXTY NINE THOUSAND SEVEN HUNDRED (1,369,700) corporate shares with a NOMINAL VALUE OF ONE THOUSAND PESETAS each, numbered correlatively from 1 through 1,369,700, accumulative and indivisible, which cannot be incorporated to negotiable instruments nor be called stock".

3.- To empower with most ample powers, the Secretary of the Board, Mr. Juan Carlos DULANTO SWAYNE, so that, on behalf and representing the Company, he appear before all necessary authorities, particularly before a Notary Public, and record officially the resolutions passed by this Meeting which in character may be registered, as well as, in general, to take all the steps necessary until obtaining the

registration of same in the Government Register of Commercial Concerns, being able to sign to such effect as many public and/or private documents as necessary without any limitation, expressly including the power to execute public documents for correction of errors, taking care to insert in the public instrument for increase of capital, all the documents required by Law, even if falling into the legal figure of self-engagement.

4.- To draw up and read the Minutes of the Meeting, which is unanimously approved and signed by the Chairman and the Secretary.

There being no further business to discuss, the Chairman adjourns the Meeting at thirteen hours on the same date."

IN WITNESS WHEREOF I ISSUE THE PRESENT CERTIFICATE WITH THE APPROVAL OF THE CHAIRMAN, IN MADRID, ON THE TWENTY-SECOND DAY OF DECEMBER, NINETEEN HUNDRED AND NINETY TWO.

Two signatures follow.----------

Approval of the CHAIRMAN
Luis Carlos RODRIGO

THE SECRETARY
Juan Carlos DULANTO

BY 0981301

M-93013-0

ARIL 6578 MADRID

LIST OF PATENTS, APPLICATION FOR PATENTS AND TRADEMARKS CONTRIBUTED BY "PROMOCIONES Y SERVICIOS INDUSTRIALES S.A." AND ASSESSMENT OF SAME.

"FEPRADINOL, HCl"

- BELGIUM:	Patent # 903.651:	Ptas. 20,000,000.
- FRANCE:	Patent # 2.573,071:	Ptas. 60,000,000.
- SWITZERLAND:	Patent # 670.823:	Ptas. 20,000,000.
- ITALY:	Patent # 1.184.670:	Ptas. 50,000,000.
- UNITED STATES:	Patent # 4.812.482:	Ptas. 147,000,000.
- PORTUGAL:	Patent # 81.479:	Ptas. 10,000,000.
- JAPAN:	Application for Patent # 60-249.089:	Ptas. 90,000,000.
SUBTOTAL:		Ptas. 397,000,000.

"2 VINCAMINE CETOGLUTARATE"

- UNITED STATES:	Patent # 3982002:	Ptas. 28,000,000.
- BELGIUM:	Patent # 823806:	Ptas. 5,000,000.
- D.F.R.:	Patent # P-2500599-6-09:	Ptas. 9,000,000.
- LUXEMBOURG:	Patent # 71545:	Ptas. 1,500,000.
- SWITZERLAND:	Patent # 593974:	Ptas. 4,000,000.
- FRANCE:	Patent # 7430299 (2283669):	Ptas. 15,000,000.
- JAPAN:	Patent # 1093823:	Ptas. 14,000,000.
SUBTOTAL:		Ptas. 76,500,000.

NOTARIO MADRID OSELUIS PRADO LOPEZ

REL. 6.578 FRANCES

E. Sofía Esteras Marqués

"CICLESONIDE"

- FRANCE:	Application for Patent # 91 10682:	Ptas. 11,500,000.
- ITALY:	Application for Patent # 91A002296:	Ptas. 8,600,000.
- UNITED KINGDOM:	Application for Patent # 9118967.0:	Ptas. 10,000,000.
- D.F.R.:	Application for Patent # P41295358:	Ptas. 14,500,000.
- GREECE:	Application for Patent#91-100353:	Ptas. 2,000,000.
- PORTUGAL:	Application for Patent # 98897:	Ptas. 2,000,000.
- HOLLAND:	Application for Patent# 9101472:	Ptas. 5,000,000.
- LUXEMBOURG:	Application for Patent # 88001:	Ptas. 700,000.
- JAPAN:	Application for Patent # 227418:	Ptas. 30,000,000.
- AUSTRALIA:	Application for Patent# 8368691:	Ptas. 5,000,000.
- SWITZERLAND:	Application for Patent #02619-913:	Ptas. 2,800,000.

- R.O.C.:	Application for Patent # 15617/91:	Ptas. 2,000,000.
- CANADA:	Application for Patent# 2.050.812-4:	Ptas. 9,300,000.
- AUSTRIA:	Application for Patent# A1769/91:	Ptas. 2,800,000.
- UNITED STATES:	Application for Patent# 578942:	Ptas. 47,000,000.
SUBTOTAL:		Ptas. 156,000,000.

"CETOVINCA"

- BENELUX:	Trademark #334058:	Ptas. 500,000.
- D.F.R.:	Trademark #951540:	Ptas. 1,000,000.
- FRANCE:	Trademark #920766:	Ptas. 2,000,000.
- ITALY:	Trademark #321876:	Ptas. 1,000,000.
- SWITZERLAND:	Trademark #279288:	Ptas. 500,000.
SUBTOTAL:		Ptas. 5,000,000.

"OXOVINCA"

- D.F.R.:	Trademark #963183:	Ptas. 1,000,000.
- FRANCE:	Trademark #924576:	Ptas. 2,000,000.
- ITALY:	Trademark #321877:	Ptas. 1,000,000.
- SWITZERLAND:	Trademark #279289:	Ptas. 500,000.
SUBTOTAL:		Ptas. 4,500,000.
TOTAL:		Ptas. 639,000,000.

NOTARIA DE DON JOSE LUIS PARDO LOPEZ

REIL 657 8 JUNIO 93

E. Sofía Esteras Mezquida
TRADUCTORA INTÉRPRETE JURADO
18-53/013-D
MADRID (España)

Translators Note:

The following pages, entitled PATENTES, numbered 1 (11) through 9 (15) are not translated upon Client's request.----------

BY 0981341

Mr. JUAN CARLOS DULANTO SWAYNE
SECRETARY OF THE BOARD OF DIRECTORS OF
"PROMOCIONES INDUSTRIALES Y SERVICIOS, S.A."

CERTIFIES:

That in the General Extraordinary Meeting of Shareholders of the company I represent, held as universal in character on December 18th, 1992, with the attendance of all the shareholders, after they unanimously accepted to hold the Meeting and the Agenda for the Day, the resolutions set forth in the Minutes of said Meeting were unanimously passed, and are transcribed literally below:

"In Madrid, at nine hours of the 18th day of December, 1992, the General Extraordinary Meeting of the Company comes to order at the Registered Offices of the Company at 15 Plaza del Conde del Valle de Suchil, with all the shareholders present representing all the corporate capital.

Those present unanimously accept to meet as General Extraordinary Meeting, Universal in character, without the requirement of advance notice, in agreement with that set forth in Article 99 of the Revised Text of the Companies Act, approved by Legislative Royal Decree 1564/89 dated December 22nd.

Having drawn up the attendance list according to that set forth in Article 111 of the Revised Text of the Companies Act and Article 98 of the Regulations of the Government Register of Commercial Concerns, attendance of all the shareholders of the Company is verified, owners of all the shares:

- SERVICIOS IBERICOS DE CONSULTORES, S.A., owner of 9,000 shares, which represent 75% of the corporate capital, represented in this act by Mr. Juan Carlos DULANTO SWAYNE by virtue of a letter of empowerment which, being found in agreement, is filed, and who is

NOTARIA DE DON JOSÉ-LUIS PAGADOR MADRID

RTL 6578 FRANG 41

E. Sofía Esteras Manzanedo
TRADUCTORA JURADA
Nº 53/01
MADRID (España)

present also as Secretary-Member of the Board of the Company and signs below.

- Mr. Juan Carlos DULANTO SWAYNE, owner of 1,500 shares representing 12.5% of the corporate capital, who equally attends as Member of the Board of the Company and who signs below.

- Mr. Luis Carlos RODRIGO MAZURE, owner of 1,500 shares representing 12.5% of the corporate capital, who equally attends as Member of the Board and President of the Company and who signs below.

With the attendance of the three aforementioned shareholders, who attend personally in the manner indicated above, the presence of all the shareholders of the Company is verified, representing all the corporate capital.

To the effect of Article 104.2 of the Revised Text of the Companies Act, acting as Chairman of the Meeting was Mr. Luis Carlos RODRIGO MAZURE and as Secretary, Mr. Juan Carlos DULANTO SWAYNE, who hold such positions within the Board of Directors.

Next the Meeting proceeds to discuss the Agenda for the Day, approving the following:

" AGENDA FOR THE DAY

1. AUTHORIZING THE INCREASE OF THE CAPITAL OF THE COMPANY "ELMUQUIMICA FARMACEUTICA, S.L."

2. DRAWING UP, READING AND SHOULD SO BE THE CASE, APPROVAL OF THE MINUTES OF THE MEETING".

The Chairman declared the Meeting validly come to upon first summons with quorum and with sufficient capacity to deal with the business included in the Agenda for the Day of the notice, and those present did not set forth any reserves or protestations regarding the

above declaration of the Chairman.

Then the Chairman suggested passing on to other business included in the Agenda for the Day, UNANIMOUSLY passing, with the aye vote of all the shares comprising the corporate capital, the following resolutions:

FIRST: They expressly empower the three members of the Board of Directors of the Company, Mr. Luis Carlos RODRIGO MAZURE, Mr. Juan Carlos DULANTO SWAYNE, and Mr. Carlos RIECKHOF DOLCI so that acting jointly whichever two of them, they may appear at the increase in capital which will take place on December 21st, 1992 in the Company "ELMUQUIMICA FARMACEUTICA, S.L." through non-monetary contribution, consisting in the presentation of patents, applications for patents and trademarks property of the Company, even if the acts for which they are empowered may entail the legal figure of self-engagement.

SECOND: To approve in this same act the Minutes of the Meeting being held, which are drawn up and read by Mr. Secretary, being then signed by the Chairman and the Secretary.

And there being no further business to discuss, the Meeting is adjourned by the Chairman at ten hours."

IN WITNESS THEREOF, I ISSUE THE PRESENT CERTIFICATE IN MADRID, ON DECEMBER 22ND, 1992.

Bears two signatures.----------

THE CHAIRMAN
Luis Carlos RODRIGO

THE SECRETARY
Juan Carlos DULANTO

THIS IS FIRST COPY EXACT AND COMPLETE OF ITS ORIGINAL, where I leave note of this Notarized Copy, which I issue upon request of

JOSE LUIS PRADO LOPEZ

E. Sofía Esteves Marqués

"ELMUQUIMICA FARMACEUTICA, S.L." in eight sheets of seventh class paper, Series OA, numbers 1.819.099 and the following seven in correlative order, in Madrid, of the day of its execution.

(Bears two illegible signatures and the stamped seal of the Madrid Notarial Offices of Maria de los Angeles Escribano Romero on each page.)

BY 0981382

22

Nº 01

DOCUMENT RECEPTION SECTION

On January 29, 1993, the party concerned presents payment voucher, promissory note 228, Cashier Register P108, settlement number ---, for the Transfer Tax. For a sum of Pesetas 6,390,000

Madrid, January 29, 1993.
The Head of the Section

(Bears illegible signature)

MARIA DE LOS ANGELES ESCRIBANO ROMERO, Notary member of the Madrid Notarial Association, with residence in the Capital City:
Certifies: That the present xerocopy comprised of 17 folios, agrees with the original which has been presented to me for identification and comparison.
Madrid, February 9, 1993.

(Bears two illegible signatures).

Translators Note:

The following page is not translated upon Client's request .

E. Sofia Esteves ... MADRID (España)

93/013-0

REEL 6578 FRAME 645

IDENTIFICATION CERTIFICATION

MARIA DE LOS ANGELES ESCRIBANO ROMERO,

Notary member of the Madrid Notarial Association, with residence in the Capital City:

Certifies: That the present copy agrees exactly with the original which is reproduced and which has been presented to me for identification and comparison.

Madrid, February 15, 1993.

(Bears two illegible signatures).

E. Sofia Esteves Marqués
TRADUCTORA [illegible]
[illegible] Tel: 359 77 31
[illegible] Madrid (España) Fax: 350 45 17

CERTIFICO que la presente es una
I CERTIFY that this is a true
traducción fiel del texto original
translation from the original
en ~~INGLES~~. / SPANISH text.
Madrid, Feb 23 1993
Fdo./Signed: E. Sofia Esteves Márquez

REEL 6578 FRAME 646

BY 0981402

LEGI../

.../TIMACION.- YO, JOSE-LUIS PARDO LOPEZ, NOTARIO DEL ILUSTRE COLEGIO DE MADRID, DOY FE: Que las treinta fotocopias unidas a éste folio, son fiel y exacta reproducción de su original que tengo a la vista. Todas ellas van extendidas en otros tantos folios de papel de los Colegios Notariales de España, serie BY., núm.: 0981845, 0981860,0981880 ,0981900 ,0981920 ,0981940 , 0981960, 0981980,0981785 ,0981810 ,0981830 ,0981018 , 0981038 , 0981058,0981078 ,0981098 ,0981117 ,0981138 , 0981181 , 0981206,0981221 ,0981241 ,0981261 ,0981281 , 0981301 , 0981321,0981341 ,0981362 ,0981382 ,0981402 , y el presente núm.: 0983586 , que dejo sellados y rubricados.----------

En Madrid, a treinta de Marzo de mil novecientos noventa y tres.----------

NOTARÍA DE DON JOSÉ-LUIS PARDO LÓPEZ MADRID

APLICACIÓN ARTº 4.3 DE 13 DE ABRIL

DOCUMENTO SIN CUANTIA

REL 6578 FRANCO 47

BY 0983586

Apostille (o legalización única)
(Convención de La Haya de 5 de octubre de 1961)
(Real Decreto 2433/1978, de 2 de octubre)

1. País: *España*

El presente documento público

2. Ha sido firmado por D. Yose Luis Pardo López

3. Actuando en calidad de *NOTARIO*

4. Se halla sellado/timbrado con *el de su Notaría*

CERTIFICADO

5. En Madrid 6. El 13 Abril 1993

7. Por el Decano del Colegio Notarial de Madrid

8. Con el número 44831

9. Sello/timbre: 10. Firma:

SELLO DE LEGALIZACIONES
25 P
VEINTICINCO PESETAS

D. Ignacio de Loyola Paz-Ares Rodríguez
Miembro de la Junta Directiva en funciones de Decano

08-11-1998

Commiss IGNMENTS Washington, D.C. 20231

FORM PTO-1595 OVER SHEET U.S. DEPARTMENT OF COMMERCE

(Rev. 6-93) 100789529 ONLY Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original document or certified copy thereof.

MAD 8-5-98

1. Name of conveying Party(ies):

ELMUQUÍMICA FARMACEUTICA, S.L.

AUG - 5 1998

PATENT & TRADEMARK OFFICE

Additional name(s) of conveying party(s) attached? ☐ Yes ☐ No

2. Name and Address of receiving Party(ies):

Name: BYK GULDEN LOMBERG CHEMISCHE FABRIK GmbH

Street Address: Byk-Gulden-Strasse 2

City: D-76467 KONSTANZ

Country: GERMANY

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: June 8, 1998

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)/Application Date

B. Patent No.(s)/Patent Date

5,482,934 issued on January 9, 1996

5. Name and address of party to whom correspondence concerning this matter should be mailed:

Jacobson, Price, Holman & Stern
400 7th Street, N.W.
Washington, DC 20004
Tel. 202-638-6666

Attorney Docket No. P57770A

6. Number of applications and patents involved: 1

7. Total fee (37 CFR 3.41)..... $ 40.00

☒ Enclosed

☒ Any deficiencies in enclosed fees are authorized to be charged to deposit account

8. Deposit Account No.: 06-1358

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and Signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

08/07/1998 DNGUYEN 00000109 5482934

01 FC:581 40.00 OP

Irwin M. Aisenberg / 19,007
Name of Person Signing / Reg.#

Signature

August 5, 1998
Date

Total number of pages including cover sheet, attachments, and document: 2

JPH&S 103-12/93

E:09US0

ASSIGNMENT

WHEREAS, ELMUQUÍMICA FARMACÈUTICA, S.L., a Spanish company having its place of business at Carretera Nacional III, Km 23, 28500 Arganda del Rey (Madrid) Spain, is the owner of the entire right, title and interest for United States Letters Patent 5,482,934, issued January 9, 1996, for PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS;

WHEREAS, the German firm of BYK GULDEN LOMBERG CHEMISCHE FABRIK GmbH of Byk-Gulden-Straße 2, D-76467 Konstanz, Germany, is desirous of acquiring the entire right, title and interest in and to said United States Letters Patent 5,482,934.

NOW, THEREFORE, in consideration of the sum of One Dollar and other good and valuable consideration paid by the said BYK GULDEN LOMBERG CHEMISCHE FABRIK GmbH to said ELMUQUÍMICA FARMACÉUTICA, S.L., of which receipt is hereby acknowledged, the said ELMUQUÍMICA FARMACÉUTICA, by its undersigned duly authorized officers, hereby sells and assigns its entire right, title and interest in and to said United States Letters Patent 5,482,934 to the said BYK GULDEN LOMBERG CHEMISCHE FABRIK GmbH, its successors and assigns.

Signed this 8 day of June, 1998.

Dr. J. Martorell

A. Ruiz Trueba

Witnessed this 8 day of June, 1998.

Dr. Montoro

Witnessed this 8 day of June, 1998.

A. Ruiz PErmuy

04-10-2003

Commissioner of Patents & Trademarks — Washington, D.C. 20231

Form PTO-1595 RE 102415996

(Rev. 03/01)

U.S. DEPARTMENT OF COMMERCE
U.S. PATENT AND TRADEMARK OFFICE

To the honorable Commissioner of Patents and Trademarks: Please record the attached original document or copy thereof:

1. Name of Conveying Party(ies):

Byk Gulden Lomberg Chemische Fabrik GmbH

4-7-03

Additional name(s) of conveying party(ies) attached? ☐ Yes ■ No

2. Name and Address of Receiving Party(ies):

Name: **Altana Pharma AG**

Street Address: **Byk-Gulden-Straße 2**

Street Address:

City: **Konstanz**

State/Country: **Germany** Postal Code: **D-78467**

Additional name(s) and addresses attached? ☐ Yes ■ No

3. Nature of Conveyance:

☐ Assignment ■ Change of Name

☐ Security Agreement ☐ Other:

☐ Merger Execution Date: **07012002**

4. Application Number(s) or Patent Number(s):

☐ Assignment is being filed together with new application and the first execution date of application is :

■ Application has been filed already and the application filing date is:

A. Patent Application Number(s):

B. Issued Patent Number(s):
5482934

Additional numbers attached? ☐ Yes ■ No

5. Name and address of party to whom correspondence concerning this matter should be mailed:

CUSTOMER NUMBER 00136 -or-

JACOBSON HOLMAN PLLC
400 Seventh Street, N.W.
Washington, D.C. 20004-2218
Tel. 202-638-6666

Attorney Docket Number: **P57770A**

6. Total number of applications and patents involved: **1**

7. Total Fee (37 CFR 3.41): **$ 40.00**

■ Enclosed

■ Any deficiencies in enclosed fees are authorized to be charged to **Deposit Account No. 06-1358.**

DO NOT USE THIS SPACE

8. Statement and Signature:

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Irwin M. Aisenberg **19,007** — Name of Person Signing, Reg. No.

Signature

April 7, 2003 — Date

Total number of pages including cover sheet, attachments, and documents: 5

JCH 103-2/02

04/10/2003 GTON11 00000018 5482934

01 FC:8 21 40.00 OP

Handelsregister – Abt. B – des Amtsgerichts Konstanz

Blatt 1

(mit Fortsetzung Blatt _____)

HRB 1925

laufende Nummer der Eintragung	a) Firma b) Sitz c) Gegenstand des Unternehmens	Grundkapital oder Stammkapital DM / EUR	Vorstand Persönlich haftende Gesellschafter Geschäftsführer Abwickler	Prokura	Rechtsverhältnisse	a) Tag der Eintragung und Unterschrift b) Bemerkungen
1	2	3	4	5	6	7
1	a. ALTANA Pharma AG b. Konstanz c. die Herstellung und der Vertrieb von und der Handel mit chemischen, pharmazeutischen, kosmetischen und diätetischen Erzeugnissen aller Art, die Errichtung, der Erwerb und der Betrieb von Fabriken und Anlagen für die Herstellung von chemischen, pharmazeutischen, kosmetischen und diätetischen Erzeugnissen und Substanzen, der Erwerb, die Vergabe und die Verwertung von gewerblichen Schutzrechten und Lizenzen sowie jede sonstige gewerblichen Beteiligung auf dem Gebiet der Industrie, des Gewerbes und des Handels im In- und Ausland. Die Gesellschaft ist berechtigt, alle Geschäfte vorzunehmen und alle Maßnahmen zu ergreifen, die mit dem Gegenstand des Unternehmens zusammenhängen oder ihm unmittelbar oder mittelbar förderlich erscheinen. Sie kann Zweigniederlassungen errichten, andere Unternehmen gründen, erwerben oder sich an solchen Unternehmen beteiligen, Unternehmensverträge abschliessen, Interessengemeinschaften eingehen und Vertretungen übernehmen.	70.000.000 €	Dr. Hans-Joachim Lohrisch, Konstanz, geb. 29.01.1949; - Vorsitzender - Andreas Görwitz, Konstanz, geb. 07.03.1956; Alfred Goll, Allensbach, geb. 17.10.1956; Prof. Dr. Heinz-Werner Radtke, Konstanz, geb. 02.07.1943; Dr. Ulrich Sorger, Konstanz, geb. 21.06.1940	Prokuristen, je gemeinschaftlich mit einem Geschäftsführer oder mit einem anderen Prokuristen vertretungsberechtigt: Dr. Herbert Suchy, Konstanz, geb. 09.02.1938; Fernando Leu, Bottighofen/Schweiz, geb. 18.03.1945; Joachim Schneider, Konstanz, geb. 29.01.1948; Dr. Lothar Bösch, Allensbach-Hegne, geb. 22.07.1950; Bernd Heuser, Konstanz, geb. 11.07.1943; Dr. Uwe Jens Oskar Schaffer, Allensbach, geb. 05.12.1941; Dr. Wilhelm Wurst, Konstanz, geb. 07.09.1948; Dr. Mohamed Bacoouche, Radolfzell, geb. 02.10.1950; Joachim Jauch, Konstanz, geb. 02.09.1955; Alexander Michler, Allensbach, geb. 24.09.1959; Dr. Ulrich Schilling, Konstanz, geb. 11.09.1951; Dr. Clive Rawson Cain, Gaienhofen-Horn, geb. 26.10.1955; Dr. Berthold Piening, Allensbach, geb. 19.11.1958	Aktiengesellschaft; aufgrund des Umwandlungsbeschlusses vom 27.05.2002 aus der Firma „Byk Gulden Lomberg Chemische Fabrik GmbH", Sitz Konstanz (bisher HR B 12 Amtsgericht Konstanz), infolge Formwechsel und Umwandlung gem. § 190 ff. UmwG. Die Satzung ist festgestellt am 27.05.2002. Zwischen der Gesellschaft und der Firma ALTANA Aktiengesellschaft, Sitz Bad Homburg v. d. Höhe (HR B 1933 Amtsgericht Bad Homburg v. d. Höhe), besteht ein Gewinnabführungsvertrag, der am 12.06.1975 mit der Firma Busch-Jaeger Gesellschaft für Industriebeteiligungen Aktiengesellschaft, Sitz Frankfurt/Main, geschlossen wurde, die durch Beschluss der Hauptversammlung vom 22.05.1979, im Handelsregister des Amtsgerichts Frankfurt/Main am 27.06.1979 eingetragen, auf die Firma ALTANA Industrie-Aktien und Anlagen Aktiengesellschaft, jetzt „ALTANA Aktiengesellschaft", Sitz Bad Homburg v. d. Höhe (HR B 1933 Amtsgericht Bad Homburg v. d. Höhe), umgewandelt worden ist und der durch eine Aktennotiz vom 06.05.1989 ergänzt wurde. Die Gesellschafterversammlung vom 20.11.1989 und die Hauptversammlung der Firma ALTANA Industrie-Aktien und Anlagen Aktiengesellschaft vom 26.06.1989 haben dem Gewinnabführungsvertrag zugestimmt. Wegen der weitergehenden Beschluss-Inhalte wird auf den Gewinnabführungsvertrag sowie auf die zustimmenden Beschlüsse der Gesellschaft Bezug genommen. Ist nur ein Vorstandsmitglied bestellt, so vertritt dieses die Gesellschaft allein. Sind mehrere Vorstandsmitglieder bestellt, so wird die Gesellschaft durch zwei Vorstandsmitglieder gemeinschaftlich oder durch ein Vorstandsmitglied in Gemeinschaft mit einem Prokuristen vertreten. Der Aufsichtsrat kann Vorstandsmitgliedern Einzelvertretungsbefugnis und/oder Befreiung von der Beschränkung des § 181 BGB erteilen.	a. 01.07.2002 Dalferich b. Anmeldung, Umwandlungsbeschluss und Satzung Sonderheft Seite 1 ff. GmbH bisher eingetragen beim Amtsgericht Konstanz unter HR B 12.

Handelsregister – Abt. B – des Amtsgerichts

Blatt _____

(mit Fortsetzung Blatt _____)

HRB 1925

a) Firma b) Sitz c) Gegenstand des Unternehmens	Grundkapital oder Stammkapital DM / EUR	Vorstand Persönlich haftende Gesellschafter Geschäftsführer Abwickler	Prokura	Rechtsverhältnisse	Tag der Eintragung und Unterschrift Bekanntmachungen
2	3	4	5	6	
			Dr. Rainer Wiartalla, Gottmadingen, geb. 24.11.1950; Franz-Peter Albrecht, Konstanz, geb. 06.05.1948; Wolf-Christian Kanzelmeyer, Allensbach geb. 13.04.1956; Dr. Ulrich Thibaut, Konstanz, geb. 12.01.1960; Prof. Dr. Volker Figala, Allensbach, geb. 25.02.1942; Hubertus Frey, Allensbach, geb. 20.06.1954.		

AMTSGER KONSTANZ

RB 111

Commercial Register — Section B — of the Local Court in Konstanz

Page 1
(with continuation page_____)

HRB 1925

No. of entry	a) Company b) Registered office c) Object of the company	Share capital or nominal capital DM / EUR	Board of management Personally liable partners Director Liquidator	Power of attorney ("Prokura")	Legal status	a) Date of entry and signature b) Remarks
1	2	3	4	5	6	7
1	a. ALTANA Pharma AG b. Konstanz. c. The manufacture and sale of and trade in chemical, pharmaceutical, cosmetic and dietetic products of all kinds, the construction, acquisition and operation of factories and plants for the manufacture of chemical, pharmaceutical, cosmetic and dietetic products and substances, the acquisition, assignment and exploitation of patent rights and licences, and any other commercial activities in trade and industry in Germany and abroad. The company is entitled to carry on any business and to take any action which is connected with the object of the company or seems directly or indirectly beneficial to it. It may set up subsidiaries, create and acquire other companies or hold shares in such businesses, enter into corporate agreements and communities of interests and act as an agent.	70 000 000 EUR	Dr. Hans-Joachim Lohrisch, Konstanz, born 29.1.1949; - Chairman - Andreas Görwitz, Konstanz, born 7.3.1966; Alfred Gell, Allensbach, born 17.10.1956; Prof. Dr. Heinz-Werner Radtke, Konstanz, born 2.7.1943; Dr. Ulrich Berger, Konstanz, born 21.6.1949	Persons holding power of attorney, authorised to represent the company jointly with a director or another person holding power of attorney: Dr. Herbert Suchy, Konstanz, born 9.2.1938; Fernando Leu, Bottighofen/Switzerland, born 16.5.1945; Joachim Schneider, Konstanz, born 29.1.1948; Dr. Lothar Bösch, Allensbach-Hegne, born 22.7.1950; Bernd Heuser, Konstanz, born 11.7.1943; Dr. Uwe Jens Oskar Schaffer, Allensbach, born 9.12.1941; Dr. Wilhelm Wurst, Konstanz, born 7.9.1948; Dr. Mohamed Baccouche, Radolfzell, born 2.10.1950; Joachim Jauch, Konstanz, born 2.8.1955; Alexander Mächler, Allensbach, born 24.9.1959; Dr. Ulrich Schilling, Konstanz, born 11.9.1951; Dr. Clive Rawson Cain, Gaienhofen-Horn, born 28.10.1955; Dr. Berthold Pleiring, Allensbach, born 19.11.1958	Public limited company. By virtue of the resolution dated 27.5.2002 to change the corporate form of the company "Byk Gulden Lomberg Chemische Fabrik GmbH", registered office in Konstanz (previously HR B 12 Local Court Konstanz), as a result of the change in corporate form and transformation pursuant to Section 190 ff UmwG [Conversion Law] The articles of association were adopted on 27.5.2002. A profit and loss transfer agreement was concluded between the company and the company ALTANA Aktiengesellschaft, registered office in Bad Homburg v. d. Höhe (HR B 1933 Local Court Bad Homburg v.d. Höhe), which was entered into on 12.6.1975 (and supplemented by a notice dated 8.8.1989) with the company Busch-Jaeger Gesellschaft für Industriebeteiligungen Aktiengesellschaft, registered office in Frankfurt/Main, which by resolution of the general meeting of 22.5.1979, entered in the Commercial Register of the Local Court Frankfurt/Main on 27.5.1979, was transformed into the company ALTANA Industrie-Aktien und Anlagen Aktiengesellschaft, now "ALTANA Aktiengesellschaft", registered office in Bad Homburg v. d. Höhe (HR B 1933 Local Court Bad Homburg v. d. Höhe). The profit and loss transfer agreement was approved by the shareholders' meeting dated 28.11.1989 and by the general meeting of the company ALTANA Industrie-Aktien und Anlagen Aktiengesellschaft dated 28.8.1989. For full details of the resolution, reference should be made to the profit and loss transfer agreement and to the resolutions of approval by the company. If only one member of the board of management is appointed, the company will be represented by him alone. If several members of the board are appointed, the company is to be represented jointly by two members of the board or by one member of the board and a person with power of attorney. The supervisory board may appoint members of the board of management with power of individual representation and/or grant exemption from the restrictions of Section 181 BGB [German Civil Code].	a. 1 July 2002 *[signed]* b. Application for registration, resolution on transformation and articles of association, special volume, Page 1 ff. GmbH registered previously at the Local Court Konstanz under HR B 12.

No. of entry	a) Company b) Registered office c) Object of the company	Share capital or nominal capital DM / EUR	Board of management Personally liable partners Director Liquidator	Power of attorney ("Prokura")	Legal status	a) Date of entry and signature b) Remarks
1	2	3	4	5	6	7
1 (contd.)				Dr. Reiner Wiartalla, Gottmadingen, born 24.11.1950; Franz-Peter Albrecht, Konstanz, born 6.6.1946; Wolf-Christian Kenzelmeyer, Allensbach, born 13.4.1956; Dr. Ulrich Thibaut, Konstanz, born 12.1.1960; Prof. Dr. Volker Figala, Allensbach, born 25.2.1942; Hubertus Frey, Allensbach, born 20.8.1954.		(Seal: The Local Court of Konstanz)
					I hereby certify that the above text is a true and correct translation of the original German document/certified copy submitted: Freiburg, dated: 23 JUL 2002 (Sworn translator)	PETER J. SPÄTH, B.A. Sworn translator and interpreter (English) for the courts of Baden-Württemberg (Germany) GLÄSSER STR. 49, D-79110 FREIBURG

EXHIBIT B

Aventis Pharmaceuticals

April 20, 2005

Cheryl Czachorowski
Senior Manager, Regulatory Affairs
ALTANA Pharma US
210 Park Avenue
Florham Park, NJ 07932

Dear Cheryl:

With this correspondence, Aventis agrees to authorize ALTANA Pharma to reference and FDA to access any information in IND 53,391 (ciclesonide metered dose inhaler) or NDA 21-658 (ALVESCO™, ciclesonide metered dose inhaler) for the review of the planned ALTANA NDA submission of the ciclesonide nasal spray (IND 65,488).

Please be advised that Aventis Pharmaceuticals considers all information in IND 53,391, NDA 21-658, and IND 48,652 to be trade secret and/or confidential commercial information exempt from public disclosure as provided in §312.130 & §20.61 of Title 21 of the Code of Federal Regulations.

If you have any questions, please don't hesitate to contact me at (908) 304-6431, or in my absence, Dr. Steve Caffé at (908) 231-5863.

Sincerely,

Daniel M. Bollag, Ph.D.
Director
US Regulatory Affairs
Aventis Pharmaceuticals Inc.

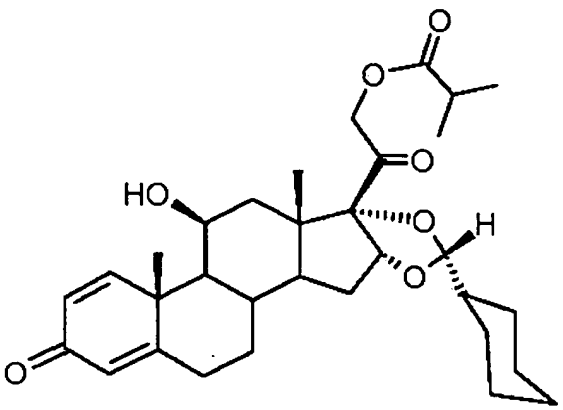
EXHIBIT C

OMNARIS

(ciclesonide)
Nasal Spray, 50 mcg
For intranasal use only

DESCRIPTION

The active component of OMNARIS Nasal Spray is ciclesonide, a non-halogenated glucocorticoid having the chemical name pregna -1,4-diene-3,20-dione, 16,17-[[R-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11β,16α)-. Ciclesonide is delivered as the R-epimer. The empirical formula is $C_{32}H_{44}O_7$ and its molecular weight is 540.7. Its structural formula is as follows:



Ciclesonide is a white to yellow-white powder, practically insoluble in water and freely soluble in ethanol and acetone. OMNARIS Nasal Spray is a metered-dose, manual-pump spray formulation containing a hypotonic aqueous suspension of ciclesonide. OMNARIS Nasal Spray also contains microcrystalline cellulose, carboxymethylcellulose sodium, hypromellose, potassium sorbate and edetate sodium; and hydrochloric acid to adjust the pH to 4.5. The contents of one 12.5 gram bottle provide 120 actuations, after initial priming. Prior to initial use, OMNARIS Nasal Spray must be gently shaken and then the pump must be primed by actuating eight times. Once primed, each actuation of the pump delivers 50 mcg ciclesonide in a volume of 70 microliters from the nasal actuator. If the product is not used for four consecutive days, it should be gently shaken and reprimed with one spray or until a fine mist appears.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclesonide is a pro-drug that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide or RM1) following intranasal application. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid receptor that is 120 times higher than the parent compound.

The precise mechanism through which ciclesonide affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic inflammation.

Pharmacokinetics

Absorption

Ciclesonide and des-ciclesonide have negligible oral bioavailability (both less than 1%) due to low gastrointestinal absorption and high first-pass metabolism. The intranasal administration of ciclesonide at recommended doses results in negligible serum concentrations of ciclesonide. However, the known active metabolite (des-ciclesonide) is detected in the serum of some patients after nasal inhalation of ciclesonide. The bioanalytical assay used has a lower limit of quantification of 25 pg/mL and 10 pg/mL, for ciclesonide and des-ciclesonide, respectively

In healthy adults treated for two weeks with 50 to 800 mcg of ciclesonide nasal spray daily (n=6 in each treatment group), the peak serum concentrations of des-ciclesonide in all subjects were found to be below 30 pg/mL. Of those treated with 800 mcg and 400 mcg daily, 100% and 67% had detectable levels of des-ciclesonide, respectively. With daily doses of 200 mcg or less, detectable serum levels of des-ciclesonide were not observed.

In pediatric subjects treated with 25 to 200 mcg of ciclesonide nasal spray daily, serum concentrations of des-ciclesonide were below 45 pg/mL, with the exception of one value of 64.5 pg/mL. In a 12-week study in children 6 to 11 years of age with perennial allergic rhinitis, des-ciclesonide was detected in 50% of the subjects treated with 200 mcg and in 5% of those treated with 100 mcg ciclesonide nasal spray daily. In a 6-week study in children 2 to 5 years of age with perennial allergic rhinitis, des-ciclesonide was detected in 41%, 22%, and 13% of the subjects treated with 200 mcg, 100 mcg, and 25 mcg ciclesonide nasal spray daily, respectively.

Distribution

Following intravenous administration of 800 mcg of ciclesonide, the volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and 12.1 L/kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged

≥ 99% each, with ≤ 1% of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.

Metabolism

Intranasal ciclesonide is hydrolyzed to a biologically active metabolite, des-ciclesonide, by esterases in the nasal mucosa. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser extent by CYP 2D6. The full range of potentially active metabolites of ciclesonide has not been characterized. After intravenous administration of ^{14}C-ciclesonide, 19.3% of the resulting radioactivity in the plasma is accounted for by ciclesonide or des-ciclesonide; the remainder may be a result of other, as yet, unidentified multiple metabolites.

Elimination

Following intravenous administration of 800 mcg of ciclesonide, the clearance values of ciclesonide and des-ciclesonide were high (approximately 152 L/h and 228 L/h, respectively). ^{14}C-labeled ciclesonide was predominantly excreted via the feces after intravenous administration (66%) indicating that excretion through bile is the major route of elimination. Approximately 20% or less of drug related radioactivity was excreted in the urine.

Special Populations

The pharmacokinetics of intranasally administered ciclesonide have not been assessed in patient subpopulations because the resulting blood levels of ciclesonide and des-ciclesonide are insufficient for pharmacokinetic calculations. However, population pharmacokinetic analysis showed that characteristics of des-ciclesonide after oral inhalation of ciclesonide were not appreciably influenced by a variety of subject characteristics such as body weight, age, race, and gender. Compared to healthy subjects, the systemic exposure (Cmax and AUC) in patients with liver impairment increased in the range or 1.4 to 2.7 fold after 1280 mcg ex-actuator ciclesonide by oral inhalation and dose adjustment in liver impairment is not necessary. Studies in renal impaired patients were not conducted.

Pharmacodynamics

In a 12-week study in children 6-11 years of age with perennial allergic rhinitis, daily doses of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray were compared to placebo nasal spray. Adrenal function was assessed by measurement of 24-hour urinary free cortisol (in 32 to 44 patients per group) and morning plasma cortisol levels (in 45 to 61 patients per group) before and after 12 consecutive weeks of treatment. The ciclesonide-treated groups had a numerically greater decline in 24-hour urinary free cortisol compared to the placebo treated group. The differences (and 95% confidence intervals) from placebo in the mean change from baseline to 12 weeks were -0.81 (-4.0, 2.4), -0.08 (-3.1, 2.9), and -2.11 (-5.3, 1.1) mcg/day for 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. The mean AM plasma cortisol value did not show any consistent treatment effect with differences

(and 95% confidence intervals) from placebo in the mean change from baseline to 12 weeks of 0.35 (-1.4, 2.1), 0.12 (-1.5, 1.7), and -0.38 (-2.1, 1.3) mcg/dL for 200 mcg, 100 mcg, and 25 mcg dose groups respectively. In this study, serum was assayed for ciclesonide and des-ciclesonide (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Absorption).

In a 6-week study in children 2 to 5 years of age with perennial allergic rhinitis, daily doses of 200 mcg, 100 mcg, and 25 mcg of OMNARIS Nasal Spray were compared to placebo nasal spray. Adrenal function was assessed by measurement of 24-hour urinary free cortisol (in 15 to 22 patients per group) and morning plasma cortisol levels (in 28 to 30 patients per group) before and after 6 consecutive weeks of treatment. The ciclesonide-treated groups had a numerically greater decline in 24-hour urinary free cortisol compared to the placebo treated group. The differences (and 95% confidence intervals) from placebo in the mean change from baseline to 6 weeks were -2.04 (-4.4, 0.3), -1.96 (-4.5, 0.6), and -1.76 (-4.3, 0.8) mcg/day for the 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. The plasma cortisol also decreased numerically after treatment with ciclesonide. The differences (and 95% confidence intervals) from placebo in the mean change in plasma cortisol from baseline to 6 weeks were -1.04 (-2.7, 0.7), -0.36 (-2.1, 1.4), and -0.12 (-1.8, 1.6) mcg/dL for the 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. In this study, serum was assayed for ciclesonide and des-ciclesonide (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Absorption).

There are no adequately conducted studies in adults and adolescents that assess the effect of OMNARIS Nasal Spray on adrenal function.

CLINICAL TRIALS

Seasonal and Perennial Allergic Rhinitis

Adult and Adolescent patients Aged 12 Years and Older:

The efficacy and safety of OMNARIS Nasal Spray were evaluated in 4 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 weeks to 1 year in duration conducted in the United States and Canada in adolescents and adults with allergic rhinitis. Three of these trials were 2 to 6 weeks in duration and primarily designed to assess efficacy. One of these trials was 1 year in duration and primarily designed to assess safety. The three trials of 2 to 6 weeks duration included a total of 1524 patients (495 males and 1029 females) of whom 79 were adolescents, ages 12 to 17 years. Of the 1524 patients, 546 patients received OMNARIS Nasal Spray 200 mcg once daily administered as 2 sprays in each nostril. Patients enrolled in the studies were 12 to 86 years of age with a history of seasonal or perennial allergic rhinitis, a positive skin test to at least one relevant allergen, and active symptoms of allergic rhinitis at study entry. Assessment of efficacy in these trials was based on patient recording of four nasal symptoms (runny nose, nasal itching, sneezing, and nasal congestion) on a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and

3=severe) as reflective or instantaneous scores. Reflective scoring required the patients to record symptom severity over the previous 12 hours; the instantaneous scoring required patients to record symptom severity at the time of recording. The results of these trials showed that patients treated with OMNARIS Nasal Spray 200 mcg once daily exhibited statistically significantly greater decreases in total nasal symptom scores than placebo treated patients. Secondary measures of efficacy were also generally supportive.

Of the three trials primarily designed to assess efficacy, one was a 2-week dose-ranging trial that evaluated efficacy of four doses of OMNARIS Nasal Spray in patients with seasonal allergic rhinitis. The primary efficacy endpoint was the difference from placebo in the change from baseline of the sum of morning and evening reflective total nasal symptom score averaged over the 2-week treatment period. Results of the primary efficacy endpoint are shown in Table 1. In this trial OMNARIS Nasal Spray 200 mcg once daily was statistically significantly different from placebo, but the lower doses were not statistically significantly different from placebo.

Table 1 Mean change in reflective total nasal symptom score over 2 weeks in patients with seasonal allergic rhinitis

Treatment	N	Baseline*	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Seasonal Allergic Rhinits Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	144	18.8	-5.73	-1.35	(-2.43, -0.28)	0.014
Ciclesonide 100 mcg	145	18.7	-5.26	-0.88	(-1.96, 0.19)	0.11
Ciclesonide 50 mcg	143	18.4	-4.82	-0.44	(-1.52, 0.63)	0.42
Ciclesonide 25 mcg	146	18.7	-4.74	-0.35	(-1.42, 0.71)	0.51
Placebo	148	17.8	-4.38			

*Sum of AM and PM Scores; Maximum score = 24

Of the other trials primarily designed to assess efficacy, one was a 4-week single dose-level trial conducted in patients with seasonal allergic rhinitis and the other was a 6-week single dose-level trial conducted in patients with perennial allergic rhinitis. The primary efficacy endpoint in the seasonal allergic rhinitis trial was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom score averaged over the first 2 weeks of treatment. The primary efficacy endpoint in the perennial allergic rhinitis trial was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom score averaged over the 6 weeks of treatment. Efficacy results of these two trials are shown in Table 2. In these trials, OMNARIS Nasal Spray 200 mcg once daily was statistically significantly different from placebo. Statistically significant differences in the morning pre-dose instantaneous total

nasal symptom score indicate that the effect was maintained over the full 24-hour dosing interval.

Table 2 Mean changes in reflective total nasal symptom score and instantaneous total nasal symptom score in allergic rhinitis trials

Treatment	n	Baseline*	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Seasonal Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	162	8.96	-2.40	-0.90	(-1.36, -0.45)	<0.001
Placebo	162	8.83	-1.50			
Seasonal Allergic Rhinitis Trial – Instantaneous total nasal symptom score						
Ciclesonide 200 mcg	162	8.45	-1.87	-0.84	(-1.30, -0.39)	<0.001
Placebo	162	8.33	-1.03			
Perennial Allergic Rhinitis Trial – Reflective total nasal symptom score						
Ciclesonide 200 mcg	232	7.59	-2.51	-0.62	(-0.97, -0.28)	<0.001
Placebo	229	7.72	-1.89			
Perennial Allergic Rhinitis Trial – Instantaneous total nasal symptom score						
Ciclesonide 200 mcg	232	7.05	-1.99	-0.53	(-0.90, -0.17)	0.004
Placebo	229	7.05	-1.46			

*Mean of AM and PM score from reflective total nasal symptom score; Mean of AM score for instantaneous total nasal symptom score; Maximum = 12

Onset of action was evaluated in two environmental exposure unit studies with a single dose of OMNARIS Nasal Spray 200 mcg. Results from these two studies did not demonstrate a replicate onset of action within the assessment period. Onset of action was also evaluated in the 4-week seasonal allergic rhinitis and in the 6-week perennial allergic rhinitis trial by frequent recording of instantaneous symptom score after the first dose. In these trials, onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis.

Pediatric Patients Aged 6 to 11 Years:

The efficacy of OMNARIS Nasal Spray at doses of 200 mcg, 100 mcg, and 25 mcg once daily was evaluated in one randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trial of 12 weeks in duration in 651 (162 – 164 per group) patients 6 to 11 years of age with perennial allergic rhinitis. The primary efficacy endpoint was the difference from placebo in the change from baseline of the average of morning and evening reflective total nasal symptom score averaged over the first 6 weeks of treatment. In this trial, none of the ciclesonide doses were statistically significantly different from placebo. The means and 95% confidence intervals for the differences (OMNARIS Nasal Spray minus

placebo) between OMNARIS Nasal Spray 200 mcg, 100 mcg, and 25 mcg treatment groups and placebo were -0.31 (-0.75, 0.13), 0.02 (-0.41, 0.46), and 0.09 (-0.35, 0.53), respectively.

INDICATIONS AND USAGE

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. Efficacy of OMNARIS Nasal Spray in children below 12 years of age has not been established.

CONTRAINDICATIONS

OMNARIS Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see **PRECAUTIONS: Pediatric Use**). Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of

intranasal corticosteroids. Patients with a known hypersensitivity reaction to other corticosteroid preparations should use caution when using ciclesonide nasal spray since cross reactivity to other corticosteroids including ciclesonide may also occur.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred. In clinical studies with OMNARIS Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS Nasal Spray. Therefore, patients using OMNARIS Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa. Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; or in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

The risk of glaucoma was evaluated by assessments of intraocular pressure in 3 studies including 943 patients. Of these, 390 adolescents or adults were treated for up to 52 weeks and 186 children ages 2 to 11 received treatment with OMNARIS Nasal Spray 200 mcg daily for up to 12 weeks. In these trials, no significant differences in intraocular pressure changes were observed between OMNARIS Nasal Spray 200 mcg and placebo-treated patients. Additionally, no significant differences between OMNARIS Nasal Spray 200 mcg and placebo-treated patients were noted during the 52-week study of adults and adolescent patients in whom thorough ophthalmologic assessments were performed including evaluation of cataract formation using slit lamp examinations. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

Information for Patients

Patients being treated with OMNARIS Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and if exposed, to obtain medical advice. Patients should use OMNARIS Nasal Spray at regular intervals since its effectiveness depends on its regular use (See DOSAGE AND ADMINISTRATION).

In clinical trials, the onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis. Initial assessment of response should be made during this timeframe and periodically until the patients symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve by a reasonable time or if the condition worsens. For the proper use of this unit and to attain maximum improvement, the patients should read and follow the accompanying patient instructions carefully. Spraying OMNARIS Nasal Spray directly into the eyes or onto the nasal septum should be avoided. It is important that the bottle is gently shaken prior to use to ensure that a consistent amount is dispensed per actuation. The bottle should be discarded after 120 actuations following initial priming or after 4 months after the bottle is removed from the foil pouch, whichever occurs first.

Drug Interactions

Based on in vitro studies in human liver microsomes, des-ciclesonide appears to have no inhibitory or induction potential on the metabolism of other drugs metabolized by CYP 450 enzymes. The inhibitory potential of ciclesonide on CYP450 isoenzymes has not been studied. In vitro studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, an inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin. In another drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Therefore, ketoconazole should be administered with caution with intranasal ciclesonide.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 times the maximum human daily intranasal dose in adults based on mcg/m^2) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 times the maximum human daily intranasal dose in adults based on mcg/m^2) in rats for 104 weeks. Ciclesonide was not mutagenic in an Ames test or in a

forward mutation assay and was not clastogenic in a human lymphocyte assay or in an in vitro micronucleus test. However, ciclesonide was clastogenic in the in vivo mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings. No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Oral administration of ciclesonide in rats up to 900 mcg/kg (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum human daily intranasal dose in adults based on mcg/m^2) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily intranasal dose based on mcg/m^2).

There are no adequate and well-controlled studies in pregnant women. OMNARIS Nasal Spray, like other corticosteroids, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids in humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Nursing Mothers

It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of ciclesonide were recovered in milk. Caution should be used when OMNARIS Nasal Spray is administered to nursing women.

Pediatric Use

Effectiveness in pediatric patients below 12 years of age has not been established (see CLINICAL TRIALS). Controlled clinical studies have shown that intranasal corticosteroids

may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including OMNARIS Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Geriatric Use

Clinical studies of OMNARIS Nasal Spray did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In controlled clinical studies conducted in the US and Canada, a total of 1524 patients ages 12 years and older received treatment with ciclesonide administered intranasally. In studies of 2 to 6 weeks duration in patients 12 years and older, 546 patients were treated with OMNARIS Nasal Spray 200 mcg daily, and in a study of up to one year in duration, 441 patients were treated with OMNARIS Nasal Spray 200 mcg daily. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. Approximately 2% of patients treated with OMNARIS Nasal Spray 200 mcg in clinical trials discontinued because of adverse events; this rate was similar for patients treated with placebo. The table below displays adverse events, irrespective of drug relationship, that occurred with an incidence of 2% or greater and more frequently with OMNARIS Nasal Spray 200 mcg than with placebo in clinical trials of 2 to 6 weeks in duration.

Adverse Events from Controlled Clinical Trials 2 to 6 Weeks in Duration in Patients 12 Years of Age and Older with Seasonal or Perennial Allergic Rhinitis

Adverse Event	OMNARIS Nasal Spray 200 mcg Once Daily (N =546) %	Placebo (N = 544) %
Headache	6.0	4.6
Epistaxis	4.9	2.9
Nasopharyngitis	3.7	3.3
Ear Pain	2.2	0.6

In a 52-week long-term safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 227 males and 436 females) with perennial allergic rhinitis, the adverse event profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse events considered likely or definitely related to OMNARIS Nasal Spray that were reported at an incidence of 1% or greater of patients and more commonly in OMNARIS Nasal Spray versus placebo were epistaxis, nasal discomfort, and headache. No patient experienced a nasal septal perforation or nasal ulcer during long-term use of OMNARIS Nasal Spray. While primarily designed to assess the long-term safety of OMNARIS Nasal Spray 200 mcg once daily, this 52-week trial demonstrated greater decreases in total nasal symptom scores with OMNARIS Nasal Spray versus placebo treated patients over the entire treatment period.

OVERDOSAGE

There are no data available on the effects of acute or chronic overdosage with OMNARIS Nasal Spray. Because of low systemic bioavailability, acute overdosage is unlikely to require any therapy other than observation. A single oral dose of up to 10 mg of ciclesonide in healthy volunteers was well tolerated and serum cortisol levels were virtually unchanged in comparison with placebo treatment. Chronic overdosage with any corticosteroid may result in signs or symptoms of hypercorticism (See PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Adults and Adolescents (12 Years of Age and Older): The recommended dose of OMNARIS Nasal Spray is 200 mcg per day administered as 2 sprays (50 mcg/spray) in each nostril once daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day). Effectiveness has not been established in pediatric patients under the age of 12 years.

Prior to initial use, OMNARIS Nasal Spray must be gently shaken and then the pump must be primed by actuating eight times. If the product is not used for four consecutive days, it should be gently shaken and reprimed with one spray or until a fine mist appears.

Directions for Use

Illustrated patient's instructions for proper use accompany each package of OMNARIS Nasal Spray.

HOW SUPPLIED

OMNARIS is supplied in an amber glass bottle and provides for nasal delivery with a manual metered pump. OMNARIS Nasal Spray is supplied with an oxygen absorber sachet and enclosed in a foil pouch. OMNARIS Nasal Spray provides 120 metered sprays after initial priming. Each spray delivers 50 mcg of ciclesonide from the nasal actuator. The OMNARIS Nasal Spray bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after removal from the foil pouch either after 120 sprays following initial priming (since the amount of ciclesonide delivered per spray thereafter may be substantially less than the labeled dose) or after 4 months. Patient instructions are also provided.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temp]. Do not freeze. **Shake gently before use.** Do not spray in eyes. **Keep out of reach of children.**

OMNARIS Nasal Spray 50 mcg, 120 metered sprays; net fill weight 12.5 g.

Rev XXXX

Manufactured for:
ALTANA Pharma US, Inc
Florham Park, NJ 07932
Made in Germany

Patient's Instructions for Use

OMNARIS (ciclesonide) Nasal Spray, 50 mcg

FOR INTRANASAL ADMINISTRATION ONLY

Please read this leaflet carefully before taking OMNARIS Nasal Spray. This leaflet does not contain the complete information about this medication. If you have any questions about OMNARIS Nasal Spray, ask your health care provider or pharmacist.

What you should know about OMNARIS Nasal Spray.

Your healthcare provider has prescribed OMNARIS Nasal Spray. It contains a medicine called ciclesonide, which helps relieve inflammation. This medication is used for the treatment of nasal symptoms associated with seasonal and year-round nasal allergy symptoms in adults and adolescents 12 years of age and older.

The nasal spray delivers your medication as an aqueous spray. Once you begin treatment, use your nasal spray once a day, every day, as prescribed by your health care provider. OMNARIS Nasal Spray may begin to work within 24 hours after the first dose. Further symptom improvements may occur over 1 to 2 weeks for seasonal allergy symptoms and 5 weeks for year-round allergy symptoms. If your symptoms do not improve in that time frame or if your condition worsens, contact your health care provider.

Dosage

The recommended dose is ***2 sprays in each nostril once daily***.

You should not use more than a total of 2 sprays in each nostril daily.

Preparing For Use

1. Remove OMNARIS Nasal Spray from its foil pouch. Count 4 months from this date and write this date (that is 4 months from removing the bottle from the foil pouch) on the sticker provided on the carton. Peel off this sticker and place it in the space provided on your nasal spray bottle. It's important to throw away the nasal spray bottle after this date.

2. Before the first use, shake the bottle gently and prime the pump by pressing downward on the shoulders of the applicator eight times. Read the complete instructions carefully and use only as directed. If you have not used the nasal spray for 4 days, shake the bottle gently and prime the pump again by spraying one time-or until a fine mist appears.

Using the Spray

1. Blow your nose to clear your nostrils if needed.

2. Shake the bottle gently and remove the dust cap.

3. Hold the bottle firmly with your index and middle finger on either side of the spray tip while supporting the base of the bottle with your thumb (Figure 1).

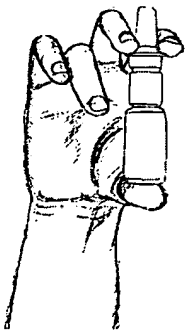


Figure 1

4. Insert spray tip into one nostril, and close the other nostril with your finger (Figure 2).

Figure 2

5. Tilt your head forward slightly and keeping the bottle upright, press the pump quickly and firmly and inhale through your nose as you spray (Figure 3). **Avoid spraying in eyes or directly onto the nasal septum (the wall between the two nostrils).**

Figure 3

6. Repeat steps 3-5 for the second spray in the same nostril and for each spray in the other nostril.

Storage Instructions

Keep your nasal spray clean and dry at all times. Store medication between 59° and 86° F. Do not freeze. Keep out of the reach of young children.

How To Know When Your Nasal Spray Bottle Is Empty

The amount of nasal spray left can be seen through a window on the bottle. Do not use this bottle for more than the labeled number of sprays or after the "discard by date" you wrote on the sticker when you opened the foil pouch. You may want to obtain a refill before your supply runs out if recommended by your health care provider.

Applicator Cleaning Instructions

After daily use of your nasal spray, wipe the applicator tip with a clean tissue and replace the dust cap.

If the nasal applicator is clogged or requires more thorough cleaning, use the following cleaning instructions **(Do not try to unblock the tiny spray hole on the nasal applicator with a pin or other sharp object)**:

1. Remove the dust cap and then gently pull upwards to free the nasal applicator.
2. Wash the dust cap and applicator with warm water.
3. Dry and replace the nasal applicator.
4. Prime the unit with one spray or until a fine mist appears.
5. Replace the dust cap.

Further Information

Avoid spraying in eyes or directly onto the nasal septum (the wall between the two nostrils).

This leaflet does not contain the complete information about your medicine. If you have any questions or are not sure about something, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

ALTANA Pharma US, Inc.
Florham Park, NJ 07932 USA

Rev. 19-Oct-06 draft

EXHIBIT D

US005482934A

United States Patent [19]

Calatayud et al.

[11] Patent Number: 5,482,934

[45] Date of Patent: Jan. 9, 1996

[54] **PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS**

[75] Inventors: **Jose Calatayud; Jose R. Conde; Manuel Luna**, all of Madrid, Spain

[73] Assignee: **Especialidades Latinas Medicamentos Universales, S.A. (Elmu, S.A.)**, Madrid, Spain

[21] Appl. No.: **278,112**

[22] Filed: **Jul. 20, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 578,942, Sep. 7, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/58**; C07J 71/00

[52] **U.S. Cl.** **514/174**; 540/63; 540/70; 552/565; 552/566

[58] **Field of Search** 540/63, 70; 514/174; 552/565, 566

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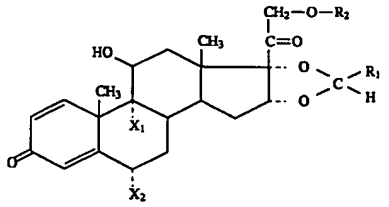
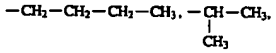
Primary Examiner—Mukund J. Shah
Assistant Examiner—Matthew V. Grumbling
Attorney, Agent, or Firm—Jacobson, Price, Holman & Stern

[57] **ABSTRACT**

The present invention relates to compounds of the formula:



in which X_1 and X_2 correspond to H or F without distinction; R_1 represents the following radicals:



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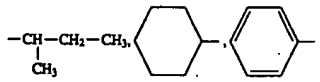
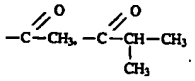


and R_2 represents the radicals



in the form of an R epimer, an S epimer, or a stereoisomeric mixture of the R and S epimers in terms of the orientation of the substituents on the carbon atom at position 22, novel intermediates and a method of their preparation by hydrolysis-ketalization, and use of such compounds as drugs and/or therapeutic agents.

12 Claims, No Drawings

PREGNA-1,4-DIENE3,20-DIONE-16-17-ACETAL-21 ESTERS, PROCESS FOR THEIR PREPARATION, COMPOSITION, AND METHODS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

This application is a continuation of application Ser. No. 07/578,942, filed Sep. 7, 1990 now abandoned.

The present invention has as its object to present pharmacologically active compounds and a process for the obtainment of said compounds and their intermediates. The invention also describes pharmaceutical compositions containing the said compounds and their use in the treatment of inflammatory conditions.

The purpose of the invention is to provide in addition certain glucocorticoids which have a combination of high anti-inflammatory activity at the application site and a low systemic glucocorticoid activity.

Since Kendall and Reichstein discovered the efficacy of cortisone in the treatment of rheumatoid arthritis (which earned them the Nobel prize), efforts have been multiplied to determine the basic structure responsible for the glucocorticoid effect and, likewise, its metabolism and mechanism of action. Since that time there have been numerous different synthetic materials which improve on the activity potential of the first product identified.

The clinical efficacy of the corticosteroids has resulted in their isolation, identification, and synthesis. The manipulation of their basic structures has permitted a wide variety of synthetic analogs, in which there has been an ongoing search for greater efficacy and an increase in the therapeutic effect/adverse systemic reaction ratio.

The toxicity effects have not been diminished, and it is important in this regard to point out that the corticosteroids are products with a clear pharmacologic effect, but with a strong power of accumulation in various tissues, which may pass unnoticed until the abrupt occurrence of a catastrophe.

In all the products studied, the therapeutic effects and the effects on the protein and carbohydrate metabolism have appeared concurrently, giving the impression that the effects sought and the adverse reactions are mediated by the same type of receptors, and that these receptors are identical for all corticosteroids.

Changes in molecular structure may cause variations in biologic activity of the corticosteroids, as a consequence of changes in absorption, protein binding, metabolism, excretion, bioavailability, and intrinsic activity in the biophase.

The introduction in -the 50's of systemic corticosteroids for the treatment of asthma constituted a milestone that was overshadowed by the appearance of side effects. This fact led to the use of corticosteroids by inhalation, since it was thought that by reducing the quantity of drug necessary to control the symptoms, it would in turn be possible to reduce the side effects. The first corticosteroid preparations developed in aerosol form were accompanied by varying efficacy and systemic side effects.

The appearance of high-activity derivatives permitted the preparation of topical formulations, with a high relative activity, combined with a low systemic action. There are two reasons for this behavior: 1) although the products can be absorbed topically, they are rapidly metabolized to less active forms; 2) the doses recommended are those which do not produce a systemic effect, not suppressing the hypothalamo-pituitary-adrenal axis within the therapeutic range used.

The corticosteroids used in aerosol form that have shown a highly positive effect are: beclomethasone dipropionate, betamethasone valerate, budesonide, flunisolide, and triamcinolone acetonide.

This philosophy of attempting to separate the local from the systemic effects has prompted the investigation of a series of corticosteroid derivatives with a distinct topical action and little or no systemic effect.

The goals of this series are decisively affected by the following factors:

a) High concentration in biophase (pulmonary or cutaneous superficial receptors)
b) Litlle topical absorption
c) Little gastrointestinal absorption
d) High sensitivity to hepatic oxidases and other inhibitory enzymes
e) Short half-life
f) Low intrinsic or systemic activity

It has been the purpose of this invention to approximate as closely as possible that drug in which all of the preceding factors merge together to produce the ideal topical corticosteroid, in the knowledge that despite its drawbacks, this therapeutic agent continues to have a great future ahead of it.

A plan has been devised to find certain corticosteroid derivatives which combine intense topical pharmacologic activity with no or minimal systemic effects.

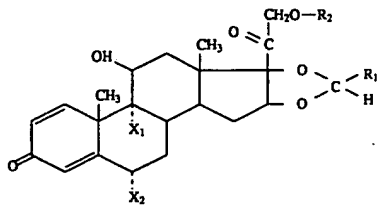
In the synthesis of 16,17-acetals of corticosteroids a mixture of epimers is obtained in relation with the formation of a new asymmetric center at C-22. The separation of the two epimers takes place through column chromatography (LC) or preparative HPLC techniques, which makes it difficult to apply industrially due to the limited quantities of product that can be treated in each unit process. In the process presented here, one of the epimers (22S)- (the most active epimer) is obtained through the hydrolysis-ketalization process from esters formed on the C-16, C- 17, and C-21 hydroxyls, wherein the ester at C-21 does not undergo hydrolysis. According to the catalyst selected it is possible to choose between obtainment of the mixture of epimers (22R,S)- or the selective obtainment of the (22S)- epimer. No process of this type has been described. European Patent Application No. 0 164 636 offers a process of transketalization from acetonides by conversion of these acetonides into acetals in the presence of aldehydes and hydrofluoric or hydrochloric acid in aqueous medium. Basically, hydrofluoric acid is used at temperatures generally ranging between 0° and −30° C., obtaining epimers of the acetals formed. No further references which describe selectivity toward one epimer or the other have been found.

The process that is the object of the invention offers [the possibility of] obtaining the (22S)- epimer or (22R,S)-mixtures of acetals from triesters previously selected while maintaining the desired radical at C-21, with these esters being easy to obtain. .The process is performed at room temperature, using solutions of dry HCl in anhydrous organic solvents. Obtainment of the R epimer is handled by preparative HPLC chromatography starting with the (22R, S)- mixture.

The steric hindrance of the acyl radical introduced and specific catalyst, makes difficult the formation of the (22S)-epimer. If the catalyst selected is extremely active, mixtures of those isomers are obtained. This hinderance characteristic is accompanied by an increase in reaction time, but does not cause a deterioration in formation of the final product by hydrolysis, secondary reactions, etc., under the conditions according to which the process takes place.

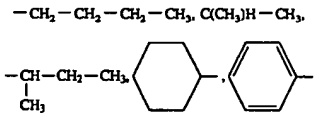
The process does not use highly corrosive or dangerous reagents, as is the case with hydrogen fluoride, nor extreme temperatures (below zero), features that are more useful for production at the industrial level.

The compounds according to the invention are characterized by the formula:

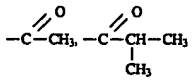


(I)

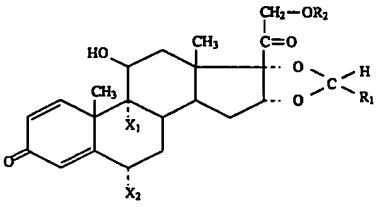
in which X_1 and X_2 correspond to H or F without distinction; R_1 represents the following radicals:



[and] R_2 represents the radicals

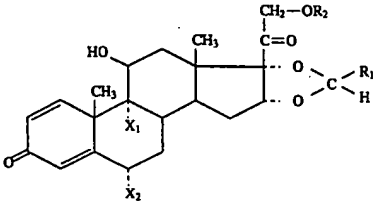


Each of these compounds has 2 stereoisomer components (epimers), which in relation to the general formula (I), may be represented in the following manner:



(II)

(S epimer)

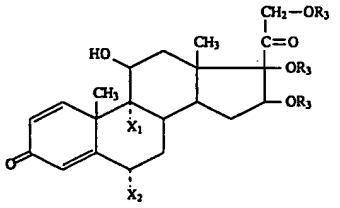


(III)

(R epimer)

In the diasteroisomers (II) and (III), the different configuration corresponds to C-22 (asymmetric carbon). These diasteroisomers take the name S and R epimers.

The compounds of this invention are prepared by hydrolysis-ketalization—with a suitable adequate catalyst which will be indicated in the corresponding cases—from the compounds triesterified at C-16, C-17, and C-21, whose structure is indicated below:



in which R_3 corresponds to an acetyl or oxo-isobutyl or isobutyryl radical and X_1 and X_2 represent H or F without distinction.

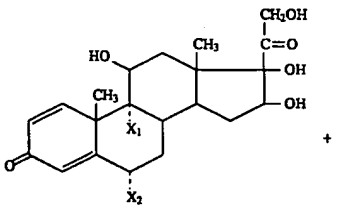
The intermediate compounds of formula IV are prepared from their corresponding hydroxylated derivatives by acylation of the appropriate anhydride in basic medium. These derivatives correspond to those with esterified hydroxyls on the carbons C-16, C-17, and C-21. The hydroxyl on carbon 11 is not esterified under the conditions whereby acylation takes place; only with certain anhydrides are small quantities on the order of 1% produced, which are treated as impurities and as such are eliminated during purification. If the quantity of anhydride present in the reaction is controlled, the ester formed on the hydroxyl of C-11 is produced in trace amounts. Thus, the number of moles of the corresponding anhydride should not exceed 25 times the number of moles of corticosteroid, so that acylation does not take place on the C-11 hydroxyl or is as restricted as possible, as has been indicated previously. The temperature of the reaction is another important factor, and the ideal conditions for acylation of the C-21, C-16, and C-17 hydroxyls are temperatures in the 15°–45° C. range. Above this temperature, a larger proportion of tetraacylated product may be obtained.

The reaction time should not exceed four hours, and the proper time for the majority of the corticosteroids and anhydrides used is from 1.5 to 2 hours.

Pyridine, dioxane, or DMSO are preferable as solvents over other possible products to obtain a greater solubility and, in particular, pyridine is the most appropriate because of its intrinsic basic character.

Once acidified and extracted with organic solvents immiscible with water, the reaction mixture is concentrated, washed, and recrystallized to obtain the corresponding compound, acylated on the C-16, C-17, and C-21 hydroxyls.

Purification by the washing and recrystallization method used gives a purity greater than 95%, which is useful for application as an intermediate product in the process for formation of the acetal according to the procedure that is the object of the invention.



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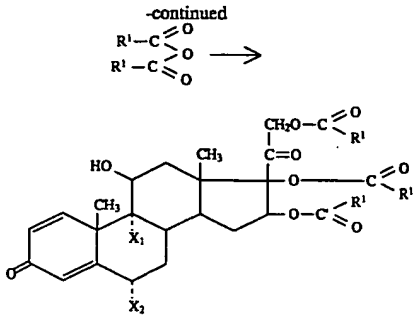


with R^1=—CH_3,

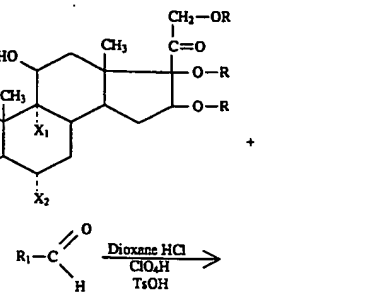
and X_1 and X_2=H, F without distinction.

The compounds represented according to formulas (I), (II), and (III) are obtained by hydrolysis of the esters at C-16 and C-17 with hydrochloric acid dissolved in the solvent which is used as a vehicle for the reaction in anhydrous medium and with a specific catalyst to direct the ketalization reaction toward the S epimer (II) or mixture of the R and S epimers (II+III) in the presence of the corresponding aldehyde. Unless otherwise clear from the text, reference to HCl gas shall mean 13% (w/w) HCl gas.

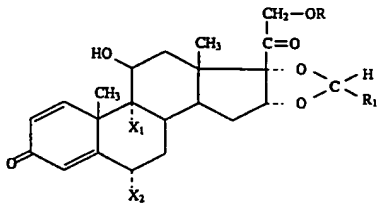
The solvents generally used are: dioxane, methylene chloride, and chloroform, all anhydrous. However, dioxane is the most widely used for this type of reaction. The selection of the solvent has a bearing on the proportion of epimers in the mixture, as milder catalysts direct the reaction toward the production of a single epimer, while more active catalysts provide a mixture of isomers that approximates the ratio of 1/1. The selection of the solvent may slightly alter this proportion. According to the epimer ratio characteristics that it is desired to obtain, the catalysts used are ρ-toluensulfonic acid, yielding the S epimer as the major product in a yield of 98–99%, and perchloric acid in 70% solution in glacial acetic acid, yielding a mixture of both R and S epimers in a ratio of 40/60 without distinction.

On conducting the reaction without catalysis, the reaction times are greatly lengthened, and therefore it is not practical to carry out the reaction under these conditions; in addition, a larger quantity of impurities is obtained. In this case, one of the isomers, the S epimer, would be obtained, present as the major portion in comparison to the R epimer.

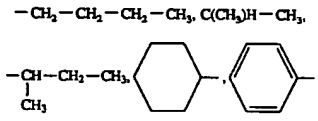
The reaction is carried out on C-16 and C-17 esters by hydrolysis in the presence of hydrochloric acid, with subsequent reaction of the aldehyde in these positions, to form the corresponding acetal. Therefore, selective hydrolysis takes place, since the ester formed at C-21 is not hydrolyzed under the conditions mentioned, so that the triester should be chosen in order to keep the radical which is of interest at C-21.



(VI)



in which R corresponds to an acetyl or oxo-isobutyl or isobutyryl radical. R_1 represents the following radicals:



The reaction is conducted at room temperature (10°–20° C.), provided that the solubility of the triester used permits it. Temperatures above 25° C. activate secondary reactions and the partial deacylation of C-21.

The reaction time fluctuates between 100 and 200 hours, depending on the starting corticosteroids, the acylating agents, and the aldehydes used, and it is necessary to reach an equilibrium between the maximum formation of the epimer or mixture of epimers and the secondary reactions that occur.

Once the excess acid has been neutralized, the crude product is extracted with methylene chloride, and the organic phase is separated, then concentrated under vacuum. The product is crystallized from ethyl ether/petroleum ether and is finally purified by treatment in a chromatographic column with LH-20 or LH-60 Sephadex as a stationary phase and a mixture of organic solvents, e.g. heptane/ethanol, or a mixture of organic solvents and water, in proportion which may range between 90/10 and 98/2 for heptane/ethanol and 70/30 for ethanol/water, as a mobile phase. There may also be subsequent purification procedures involving washing or reprecipitation with solvents such as methanol, ethanol, acetone, dioxane, ethyl acetate, water etc. By using these one at a time or in binary or ternary mixtures such as dioxane/water or ethanol/acetone/water in appropriate proportions, purification son the order of 99.5-99.9% are obtained. Thus in our case, we achieved a purification process with ternary mixtures of ethyl alcohol/acetone/water which, by dissolution of the product in organic solvents and subsequent precipitation by addition of the corresponding

proportion of water under very specific, very vigorous agitation conditions and very slow addition time, among other factors, results in purification from an 85-90% starting point to 99.99% purity.

Purification by column chromatography is not suitable for industrial production. In this type of operation there are usable fine industrial purification methods which make the obtainment process for this type of compound very complete.

Depending on the application site, and with the purpose of achieving optimal availability of the active ingredient, different galenical formulations have been prepared for topical administration of the compounds according to this invention.

Optimal availability for percutaneous formulations is achieved with a system of glycol-based solvents (propylene glycol and 1,3-butanediol) alone or in combination with water. It is also possible to dissolve the steroids completely or partially in a lipophilic phase, with the aid of a surfactant as a solubilizer. Percutaneous compositions come in the form of ointments, oil-water cream, water-oil cream or lotion. The active principle may be present in the previous pharmaceutical compositions in solution, in continuous dispersed phase, or as micronized solids.

The aerosol system is designed in such a way that each delivered dose contains 10–1000 μg (preferably 20–250 μg) of the active steroid. The most active steroids are administered in the lower part of the dosage range. The micronized steroid must be in particles substantially smaller than 5 μm. In the pressurized acrosol, the substance is suspended in a propellant gas mixture with the assistance of a dispersant, such as sorbitan trioleate, oleic acid, lecithin, or sodium salt of dioctylsulfosuccinic acid.

The invention will be further illustrated by the following non-limitative examples. The molecular weights of the corresponding products have been confirmed by mass spectrometry, and the melting points (uncorrected) determined with a Buchi unit. The HPLC analyses were performed under the following conditions:

Apparatus:	Hewlett-Packard 1084 A
Detector:	UVD (243 mn vx. 430 nm)
Column:	200 x 4.6 mm
Stationary phase:	Lichrosorb C18 (5 μm)
Mobile phase:	Ethanol: Water (0.5 ml/min)
Temperature:	35° C.
Injection:	5 μl ethanol sol. at 2 mg/ml

SYNTHESIS OF TRIACYLATED DERIVATIVES C-16, C-17, AND C-21

EXAMPLE I

Preparation of pregna 1,4-diene-3,20-dione, 16,17,21-tris-(2-methyl-1-oxo-propoxy)- 11-hydroxy (11β,16α)

30 ml pyridine and 21.6 g isobutyric anhydride (equivalent to 0.13 moles) are placed in a 500 ml reactor equipped with mechanical agitation; while agitating vigorously, 10 g (0.026 mole) pregna-1,4-diene-3,20-dione, 11,16,17,21-tetrahydroxy (11β,16α) are added gradually in portions at room temperature. The corticosteroid addition time corresponds to approximately 25–30 min. Once the said corticosteroid has been dissolved at room temperature, agitation is continued for a period of time ranging between 1.5 and 2 hr until esterification of the hydroxyls at C-21, C-16 and C-17 is complete. Upon completion of the reaction, 150 ml of a 10% aqueous solution of HCl are added, and agitation of the reaction mixture is continued for 30 min.; subsequently, the said mixture is treated three times with the 88 ml methylene chloride in order to extract the triester, and the organic phase is washed three times with 100 ml water each time. The solution is concentrated under vacuum in a rotary evaporator, and produces a crude product which is treated with 50 ml ethyl ether and 200 ml petroleum ether (fraction 40/60). Agitation of the precipitate obtained is continued for 1 hr., and finally the product is filtered and recrystallized with petroleum ether (40/60/ethyl ether 4/1, obtaining a yield of 13.3 g and a purity of 97.5– 98%.

TLC: Toluene/ethyl acetate 30/40, Rf=0.61.

EXAMPLE II

Preparation of pregna 1,4-diene-3,20 dione-16,17,21-tris-(2-methyl-1, oxo-propoxy)- 6,9-difluoro-11-hydroxy (6α,11β,16α)

80 ml pyridine 19.2 g (0.12 mole) isobutyric anhydride are placed in a 500 ml reactor, and gradually, with the reaction mixture maintained at 40° C., 10 g (0.024 mole) pregna-1,4-diene-3,20-dione, 6,9-difluoro-11,16,17,21-tetrahydroxy (6α,11β,16α) are introduced in such a way that no further quantity is added until the previous portion has dissolved. The fluocinolone dissolution time is equivalent to approximately 2 hr. Once dissolved, agitation of the solution is continued for 3 hr. at 40° C. The TLC of the reaction mixture indicates when all of the corticosteroid has reacted. Once the indicated time has elapsed, the product is cooled and 80 ml of an aqueous solution of 10% hydrochloric acid ar added after cooling has been achieved. The reaction mixture is extracted 4 times with 40 ml chloroform each time, the chloroform extract is washed 4 times with 40 ml water, and the extract is dried over $MgSO_4$. It is then brought to dryness in a rotary evaporator, and precipitated and recrystallized with ethil ether petroleum ether (40/60 fraction), obtaining a yield of 12.1 g and a purity of 95%.

TLC solvent: toluene/ethyl acetate 30/40, Rf=0.48.

EXAMPLE III

Preparation of pregna 1,4-diene-3,20-dione, 16,17,21-tris-(2-methyl-1-oxo-propoxy)- 9-fluoro-11-hydroxy-(11β, 16α)

The process applicable to the triester of triamcinolone isobutyrate is similar to the preceding process.

EXAMPLE IV

Synthesis of pregna 1,4-diene-3,20-dione, 16,17,21-tris-(acetyloxy)-11-hydroxy-(11β,16α)

In a 500 ml reactor equipped with a mechanical agitator and addition funnel, 10 g (0.026 mole) pregna- 1,4-diene-3,20-dione, 11,16,17,21-tetrahydroxy (11β,16α) are dissolved in 30 ml pyridine with vigorous agitation. 13.5 g (0.13 mole) acetic anhydride are introduced in such a way that the addition takes place within 10 min. and the temperature of the reaction mixture does not exceed 20° C. Once the acetic anhydride has been added, agitation is continued for 1 hr. (TLC or HPLC on a sample will indicate the end of the reaction by the disappearance of the starting corticosteroid). The reaction time should not be extended beyond the indicated period in order to prevent acylation on the C-11 hydroxyl. Upon completion of the reaction, 130 ml of a 10% aqueous solution of HCl are added, maintaining the reaction mixture for 30 min. with agitation. Subsequently, three

times, 75 ml methylene chloride (each time) are added to extract the triester formed. The solution of the organic extract is washed 3 times with 100 ml water (each time), and is maintained for 12–14 hr. with anhydrous $MgSO_4$ to dry the said solution.

Concentration to dryness of the organic extract gives an oil which is treated with ethyl ether/petroleum ether (40/60 fraction) 1/3. The precipitate obtained is recrystallized from methylene chloride/petroleum ether 1/4, obtaining 12.5 g pregna-1,4-diene-3,20-dione, 16,17,21-tris-(acetyloxy)-11-hydroxy (11β,16α) of 98–98.5% purity.

EXAMPLE V

Formation of pregna 1,4-diene- 3,20-dione-16,17,21-tris (acetyloxy)-6,9-difluoro- 11-hydroxy-(6α,11β,16α)

10 g pregna-1,4-diene-3,20-dione-6,9-difluoro- 11,16,17, 21-tetrahydroxy-(6α,11β,16α) (0.024 mole) are dissolved in 110 ml pyridine heated to 50° C. to facilitate dissolution in a 500 ml reactor, equipped with mechanical agitation, a thermometer, and an addition funnel; the mixture is cooled, and once the corticosteroid is completely dissolved, 19.4 g (0.19 mole) acetic anhydride are slowly added with vigorous agitation (45° C.), continuing to stir for 3 hr. and subsequently for 1 hr. more at 45° C. This time period can be extended somewhat. A sample in TLC or by HPLC will indicate the end of the reaction. Subsequently, 300 ml aqueous solution of 10% HCl are introduced, continuing to stir the mixture for 45 min.; finally, the triester formed is extracted three times with 80 ml methylene chloride (each time), and the organic extract is kept over $MgSO_4$. The solution is evaporated to dryness, and the oil obtained is treated with 50 ml ethyl acetate and 150 ml petroleum ether (40/60 fraction) with agitation for 1 hr.

The precipitate obtained is recrystallized in ethyl ether/petroleum ether 1/4, obtaining 11.8 g pregna-1,4-diene-3,20-dione-16,17,21-tris-(acetyloxy)- 6,9-difluoro-11-hydroxy-(6α,11β,16α) with a purity of 96.5%.

EXAMPLE VI

Preparation of pregna 1,4-diene-3,20-dione, 16,17,21-tris-(acetyloxy)-9-fluoro- 11-hydroxy (11β,16α)

This synthesis takes place in the same way as indicated previously, giving similar yields and purities.

When the triacylated derivatives are treated with dioxane, containing 13–15 wt % HCl gas in solution and the corresponding aldehyde in the presence of 70% perchloric acid in glacial acetic acid as a catalyst, under the temperature and time conditions specified in the following examples, the corresponding acetal is obtained on the C-16 and C-17 hydroxyls, with a mixture of R and S epimers which fluctuates between 40/60%, 50/50% according to the conditions under which the reaction is conducted. If, in contrast, p-toluenesulfonic acid is used as a catalyst instead of the perchloric acid mentioned earlier, the S epimer is obtained predominantly in a quantity of 95–98%. In both cases, the ester at C-21 does not undergo hydrolysis.

The structure of the synthesized compounds and their most significant spectroscopic characteristics are summarized in Table I.

The processes for obtainment of mixture of epimers and processes for formation of the S epimer are described separately in the following non-limiting examples of the invention.

FORMATION OF (22R,S-) AND (22S)- DERIVATIVES

EXAMPLE VII

Synthesis of (22R,S)- pregna 1,4-diene-3,20-dione, 16,17-[[cyclohexylmethylidyne]bis (oxy)] -11-hydroxy-21-(2-methyl-1-oxo-propoxy)-(11β,16α)

55 ml anhydrous dioxane are placed in a 500 ml reactor provided with mechanical agitation and an addition funnel, and 8 g (0.014 mole) pregna-1,4-diene 3,20-dione, 16,17, 21-tris-(2-methyl-1-oxo-propoxy)- 11-hydroxy-(11β,16α) and 4.3 g (0.038 mol) of cyclohexane carbaldehyde are dissolved in it; subsequently the mixture is stirred for 30 min., and 45 ml dioxane HCl containing 13% HCl gas are added slowly, and finally, dropwise, 1 ml 70% perchloric acid in glacial acetic acid (taking on a reddish color) is kept for 190 hr. with agitation and then heated to 40° C. for 12 hr. It is possible to estimate whether the reaction is complete with an aliquot of the reaction product, analyzing a sample by HPLC under the conditions stipulated below.

Once the triester has disappeared from the reaction mixture, the reaction is considered to be terminated; adding 200 ml methylene chloride, the mixture is treated with 500 ml 5% K_2CO_3 in aqueous solution, with vigorous agitation in a separatory funnel, and the organic mixture is washed three times with 80 ml water (each time). Once decanted, the organic phase is kept over on anhydrous $MgSO_4$ for drying, and is concentrated to dryness on a rotary evaporator; an oil remains, which upon treatment with 25 ml methylene chloride and 150 ml petroleum either (40/60 fraction) yields 8.52 g crude product which is purified either by recrystallization in ethyl ether/petroleum ether or by passing through a column with Sephadex LH-20 as the stationary phase and ethanol-free chloroform as the mobile phase, obtaining 8 g (22R,S)-pregna-1,4-diene-3,20-dione, 16,17-cyclohexyl-methylidyne-bis(oxy)-11-hydroxy-21-(2-methyl- 1-oxo-propoxy)-(11β,16α) in a purity of 98.5–99% and with an epimer proportion of 45/55% to 50/50%.

The mixture of epimers is resolved by preparative HPLC, using a 7 μm Lichrosorb RP-18 column (250×10 mm i.d.) and ethanol/water as the mobile phase, and obtaining the (22R)- epimer practically pure and the (22S)- epimer in a purity greater than 99%.

The product containing the (22R,S)- mixture can also be purified without having to use column chromatography by a method which is described in the following example.

EXAMPLE VIII

Obtainment of (22,S)- pregna 1,4-diene-3,20-dione 16,17-[[cyclohexyl-methylidyne]bis (oxy)]- 11-hydroxy-21-(2-methyl-1-oxo-propoxy)-(11β,16α)

55 ml anhydrous dioxane are placed in a 500 ml reactor and 8 g (0.014 mole) pregna-1,4-diene-3,20-dione, 16,17, 21-tris-(2-methyl-1-oxo-propoxy)-(11β,16α)- and 4.3 g (0.038 mole) cyclohexane carbaldehyde are dissolved, next adding 1 g p-toluenesulfonic acid and 50 ml dioxane-HCl (containing 13% HCl gas), which is introduced slowly over a period of 30 min. Agitation is continued for 200 hr., and the end of the reaction may be estimated by analyzing the mixture of HPLC under the conditions indicated below. Once the acetal is formed, 200 ml CL_2CH_2 are added to the reaction mixture and treated with 500 ml 5% K_2CO_3 in aqueous solution to eliminate the acidity. Following this elimination, the product is washed three times with 80 ml water; the solution is dried over $MgSO_4$ and brought to dryness in a rotary evaporator. The oil obtained is treated with 25 ml CL_2CH_2 and 50 ml petroleum ether (40/60 fraction). The solid collected, 5.3 g,. is purified by the method described below.

5.2 g of crude are dissolved in 300 ml 96° ethanol and 50 ml acetone in a 500 ml flask provided with vigorous mechanical agitation and an addition funnel. 80 ml water are slowly added dropwise with vigorous agitation, so that the addition process is completed within 6 hrs. Once all the water has been added, the precipitate formed is stirred for 2 hrs., filtered and washed with water, and the product dried in a 40° oven, obtaining 4.5 g (22S)- pregna-1,4-diene,3,20-dione, 16,17-cyclohexylmethylidyne-bis(oxy)-11-hydroxy-21-(2-methyl-1-oxo-propoxy)-(11β,16α) in a purity greater than 99%.

This method is extended, with small variations, to purification of the remaining compounds, and is not limited to the examples indicated. It is also possible to employ column purification using Sephadex LH-20 as the stationary phase and ethanol-free chloroform as the mobile phase. Within this purification there is a first very pure fraction of the S epimer and a second fraction in which the ratio of R and S isomers may fall in the range of 2/98%, respectively.

EXAMPLE IX

Formation of (22R,S)- of pregna 1,4-diene- 3,20-dione-21-(acetyloxy)-11-hydroxy-16,17-(pentylidene) bis(oxy)-(11β,16α)

8 g (0.016 mole) pregna-1,4-diene-3,20-dione- 16,17,21-tris-(acetyloxy)-11-hydroxy-(11β,16α) are dissolved in 60 ml anhydrous dioxane in a 500 ml flask, provided with a thermometer, mechanical agitation, an addition funnel and waterbath; subsequently, 4 g (0.046 mole) valeraldehyde are added and, slowly, dropwise, with vigorous agitation, 60 ml dioxane HCl (containing 13% HCl gas). Once addition of the dioxane is complete, 1 ml 70% perchloric acid in glacial acetic acid is introduced, heating the product to 50° C. for 200 hrs. Running a sample through TLC or HPLC will indicate whether the reaction is complete by the appearance of two peaks of the epimers and the disappearance of the triester of the reaction. Upon completion of ketalization, 175 ml chloroform are added, vigorously agitating the mixture in a separatory funnel with 510 ml aqueous solution of 5% K_2CO_3. If a pH below 6 persists in the organic phase, additional treatment with an aqueous solution of K_2CO_3 is performed until the excess acidity is eliminated. The organic phase is washed three times with 100 ml water (each time), and is kept for 14 hr. over $MgSO_4$; the filtered organic phase is brought to dryness in a rotary evaporator, yielding an oil which when treated with 50 ml ethyl ether and 170 ml petroleum ether (40/60 fraction) gives a crude solid of 6.5 g.

The following procedure is performed for the purification of this product:

A mixture of 39 ml acetone, 65 ml 96° ethanol, and 104 ml water are placed in a 250 ml flask, and 6.5 g of the crude product obtained previously are suspended while agitating vigorously, and this agitation is continued for 3 hr.; the product is then filtered, washed with water, and dried in an oven at 45° C., giving 5.7 g (22R,S)- pregna-1,4-diene-3,20-dione, 21-(acetyloxy)- 11-hydroxy-16,17-(pentylidene)-bis-(oxy)-(11β,16α) in a purity of 99.5%. The ratio of R/S epimers is 45/55.

The resolution of the epimers is achieved similarly according to the characteristics indicated in Example VII.

EXAMPLE X

Formation of (22S)- pregna 1,4-diene-3,20-dione-21-(acetyloxy)-11-hydroxy- 16,17-(pentylidene)-bis-(oxy)-(11β,16α)

8 g (0.016 mole) pregna-1,4-diene-3,20-dione, 16,17,21-tris-(acetyloxy)-11-hydroxy-(11β,16α) are dissolved in 65 ml anhydrous dioxane in a 500 ml reactor provided with mechanical agitation and an addition funnel, and subsequently 4 g (0.046 mole) valeraldehyde and 1.2 g p-toluenesulfonic acid are introduced, followed by the dropwise addition with vigorous agitation of 60 ml dioxane-HCl (13 wt % HCl). Once added, agitation of the product is continued at 50° C. for the period of time necessary for the triester to disappear from the reaction mixture. The reaction is followed by HPLC, whereby the formation of the S epimer is visualized perfectly. TLC only reveals elimination of the triester, so that the first method is more advisable. The reaction time fluctuates between 100 and 150 hr. The reaction mixture is then treated with 120 ml chloroform and 60 ml methylene chloride. The organic solution is treated with a 5% K_2CO_3 solution in order to eliminate the excess acidity and is washed three times with water; the residual water is eliminated by allowing it to stand over anhydrous $MgSO_4$. The organic phase is brought to dryness, and the crude product in the form of an oil is treated with a mixture of 25 ml ethyl ether, 25 ml methylene chloride, and 175 ml petroleum ether (40/60 fraction). 4.5 g solid are obtained, which is purified according to the method followed in the preceding example.

EXAMPLE XI

Formation of (22R,S)- pregna 1,4-diene- 3,20-dione-16,17-(cyclohyxyl methylidine)-bis-(oxy)-6,9-difluoro-11-hydroxy-21-(methyl- 1-oxo-propoxy)-(11β,16α)

100 ml anhydrous dioxane heated on a water bath to 35° C. are placed in a 500 ml reactor equipped with a water bath, addition funnel, and mechanical agitation; under agitation, 8.8 g (0.014 mole) pregna- 1,4-diene-3,20-dione, 16,17,21-tris-(2-methyl-1-oxo-propoxy)- 6,9-difluoro-11-hydroxy-(6α,11β,16α) are added in small portions while agitating (a portion of the triester should not be added until the previous fraction has dissolved completely). Once all of the triester has been added and dissolved completely, the product is kept between 15°-18° C. for several minutes while agitating, and 4.5 g (0.04 mole) cyclohexane carbaldehyde and 1.1 ml 70% perchloric acid in glacial acetic acid are added. Finally, 50 ml anhydrous dioxane containing 13–14% HCl gas by weight is slowly added and continuously stirred at room temperature during the time necessary for the triester to disappear from the reaction mixture. Once the reaction is complete, 250 ml chloroform are added; the mixture is treated three times in a separatory funnel with 250 ml of a 5% aqueous solution of K_2CO_3 each, and washed again three times with 100 ml water each time. The organic phase is kept over anhydrous $MgSO_4$ or another suitable drying agent; the organic solution is concentrated to about ⅓ of its volume and is treated with 300 ml ethyl acetate, continuing to stir the mixture for 2 hr. at 30° C. Subsequently, the solution is cooled and kept overnight at −10° C. Finally, it is concentrated to dryness, and the oil obtained is treated with 50 ml ethyl ether and 180 ml petroleum ether. The solution is kept cold during 24 hr., yielding a precipitate of 7.5 g (22R,S)- pregna-1,4-diene-3,20-dione, 16,17-(cyclohexylmethylidine)-bis-(oxy)-6,9-difluoro- 11-hydroxy-21 (methyl-1-oxo-propoxy)-(11β,16α). This product can be purified by the method indicated in Example VIII, and in this manner a yield of 7 g is obtained, with a purity of 99–99.5% and a proportion of R/S epimers of approximately 40/60%.

The resolution of the epimers is achieved similarly according to the characteristics indicated in Example VII.

EXAMPLE XII

Formation of (22S)- pregna-1,4-diene- 3,20-dione-16,17-(cyclohexylmethylidine)-bis-(oxy)- 6,9-difluoro-11-hydroxy-21-(s-methyl- 1-oxo-propoxy)-(11β,16α)

120 ml anhydrous chloroform, 4,5 g (0.04 mole) cyclohexane carbaldehyde and 1 g ρ-toluenesulfonic acid are placed in a 1 L reactor provided with a water bath, a reflux condenser, a Dean-Stark trap, a magnetic stirrer, thermometer and addition funnel. While vigorously agitating and in aliquots 8.8 g (0.014 molc) pregna-1,4-dienc-3,20-dione, 16,17,21-tris-(2-methyl- 1-oxo-propoxy)-6,9-difluoro-11-hydroxy (6α,11β,16α) are added in small aliquots in such a way that no new aliquot is added until the previous one has been dissolved. Finally, 100 ml chloroform containing HCl gas dissolved in an approximate proportion of 10 wt % are added, and the product is kept under vigorous agitation for 5 hr. at room temperature. Subsequently, the product is maintained under very mild reflux (water is collected in the Dean-Stark trap during the process) along the time necessary for the reaction to be completed, i.e., until no more triester exists in the reaction mass. This can be checked by taking a small sample from the reactor, first neutralizing it, and then estimating the end of the reaction by HPLC. It is advisable to add an additional 10–15 ml chloroform-hydrochloric acid during the process.

200 ml methylene chloride are added to the reaction mixture; the mixture is treated three times with 200 ml 5% K_2CO_3 in aqueous solution, and subsequently washed three times with 80 ml water each time. The organic solution is left overnight, drying with anhydrous $MgSO_4$ or another conventional drying agent, brought to dryness, and the oil obtained is treated with 200 ml toluene for 2 hr., with agitation. The oil is collected by decantation and is diluted in 50 ml methylene chloride and 20 ml tert-methyl-butyl ether, and the solution obtained is precipitated with 75 ml petroleum ether (40/60 fraction), increasing the quantity of the said ether (if necessary) up to the point of complete precipitation. It is advisable that he petroleum ether be added slowly, with vigorous agitation. The solid collected, 7.2 g, is purified by the following procedure. 7.2 g of the product obtained previously are dissolved in a flask which contains 150 ml 96° ethanol and 200 ml acetone; under stirring vigorously, 200 ml water are added slowly, dropwise, so that complete addition of the water is achieved within 6 to 7 hr. The precipitate formed is stirred for 2 hr., after which the precipitate obtained is filtered and washed with water and dried in a 40°–45° C. oven, given 6.5 g pregna-1,4-diene-3,20-dione, 6,17-(cyclohexylmethylidine)-bis(oxy)-6,9-difluoro- 11-hydroxy-21(2-methyl-1-oxo-propoxy)-(11β,16α) in a purity above 99%. The ratio of the R/S isomers corresponds to 1/99%, respectively.

A similar process is that followed in the formation of the different acetals of pregna-1,4-diene- 3,20-dione, 11,16,17, 21-tetrahydroxy-(11β,16α), pregna- 1,4-diene-3,20-dione, 9-fluoro-11,16,17,21-tetrahydroxy-(11β,16α), and pregna-1,4-diene-3,20-dione, 6,9-difluoro- 11,16,17,21-tetrahydroxy-(6α,11β,16α) with valeraldehyde, cyclohexanecarbaldehyde, benzaldehyde, isobutyraldehyde, and isovaleraldehyde for the formation of the 21-esters (22R,S)- (22S)- of the corresponding compounds, and it is possible by preparative HPLC to achieve the separation of (22R)- and (22S)- from the mixture.

The structure of the compounds synthesized and their most significant spectroscopic properties are compiled in Table II.

EXAMPLES OF PHARMACEUTICAL PREPARATIONS

The following and non-limitative examples illustrate the formulations intended for different topical forms of administration. The amount of active steroid in the percutaneous formulations are ordinarily 0.001–0.2% (w/w) preferably 0.01–0.1% (w/w).

Formulation 1, Ointment	
Steroid micronized	0.025 g
Liquid paraffin	15 g
White paraffin a.d.	100.0 g
Formulation 2, Ointment	
Steroid	0.025 g
Propylene glycol	6.0 g
Arlacel 83 (sorbitan sesquioleate)	6.0 g
Liquid paraffin	15.0 g
White paraffin a.d.	100.0 g
Formulation 3, O/W Cream	
Steroid	0.025 g
Cetyl alcohol	7.0 g
Glyceryl monostearate	4.0 g
Soft paraffin	15.0 g
Polyglycol 1500	3.0 g
Citric acid	0.1 g
Sodium citrate	0.2 g
Propylene glycol	20.0 g
Water a.d.	100.0 g
Formulation 4, O/W Cream	
Steroid micronized	0.025 g
Soft paraffin	20.0 g
Liquid paraffin	5.0 g
Cetyl alcohol	5.0 g
Tween 65	3.0 g
Span 60	1.0 g
Citric acid	0.1 g
Sorbic acid	0.2 g
Sodium citrate	0.2 g
Water a.d.	100.0 g
Formulation 5, W/O Cream	
Steroid	0.025 g
Soft paraffin	35.0 g
Liquid paraffin	8.0 g
Arlacel 83	5.0 g
Sorbic acid	0.2 g
Citric acid	0.1 g
Sodium citrate	0.2 g
Water a.d.	100.0 g
Formulation 6, Lotion	
Steroid	0.025 g
Isopropanol	50.0 ml
Carbopol 940	0.5 g
NaOH	q.s.
Water a.d.	100.0 g
Formulation 7, Injectable suspension	
Steroid Micronized	0.05–10 mg
Sodium carboxymethylcellulose	7 mg
Sodium chloride	10 mg
Tween 80	0.5 mg
Benzyl alcohol	8 mg
Water for injection	1.0 ml
Formulation 8, Pressurized Aerosol for Oral and Nasal Inhalation	
Steroid micronized	0.1% w/w
Sorbiton trioleate	0.7% w/w
Thrichloro-fluoromethane	24.8% w/w
Dichloro-tetrafluoroethane	24.8% w/w
Dichlorodifluoromethane	49.6% w/w
Formulation 9, Solution for Atomization	
Steroid	7.0 mg
Propylene glycol	5.0 g
Water a.d.	10.0 g

-continued

Formulation 10, Powder for Inhalation A capsule filled with a mixture of	
Steroid micronized	0.1 g
Lactose	20 mg

PHARMACOLOGIC TESTS

All of the steroids described in this invention are pharmacologically active compounds. The glucocorticoid activity of these products was studied in comparison with that of budesonide: pregna-1,4-diene- 3,20-dione, 16,17-butylidenebis(oxy)-11-21-dihydroxy-(11β,16α). The pharmacologic action on the acetonides triamcinolone acetonide and flunisolide was also studied.

Anti-inflammatory effects of the compounds were screened in the cotton pellet granuloma bioassay for identification of lead compounds. (Meier et al., *Eperimentia* 6, 469, 1950). Male Wistar rats were used, ranging in weight between 90 and 120 g, at the rate of 10 animals per group, previously identified and quartered in individual cages. The animals had free access to feed and drink throughout the trial.

Cotton pellets weighing exactly 20 mg were prepared, sterilized for 2 hr. at 160° C. soaked with 50 λl solution of the product or with the solvent before implantation, and subsequently the solvent is evaporated before application. The implantation was performed subcutaneously in the axillary zone of the animals previously anesthetized with ether (right axilla pellet with product, left axilla pellet with solvent). Animals in which pellets without product were implanted were used as controls.

The drug was applied in alcohol solution at 4 dosage levels. Once the pellets were implanted, the animals were kept under normal rearing conditions, isolated for 7 days and then weighed, after which they were sacrificed by exsanguination.

Extraction and weighing of the thymus and adrenals were performed in all animals and a fluorometric determination of the cortisol plasma levels was made. We consider the variation in these parameters indicative of the systemic glucocorticoid activity of the products.

The topical activity was determined by the inhibitory effect on the weight of the cotton-pellet-induced granuloma; the granulomas were extracted and weighed (pellet and connective tissue surrounding them, dried for 24 hr in a 60° oven, and weighed).

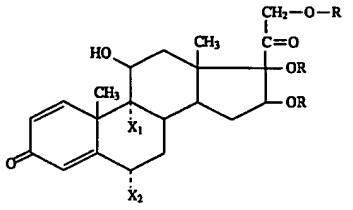
The results are in the Tables IIIa and IIIb.

Anti-inflammatory ED_{50} (topical effect), thymus inhibition ED_{50} (systemic effect), therapeutic index (systemic ED_{50}/topical ED_{50}), and the therapeutic index relative to budesonide (=1).

All of the ED_{50} values were calculated from the linear regression lines with the confidence limits.

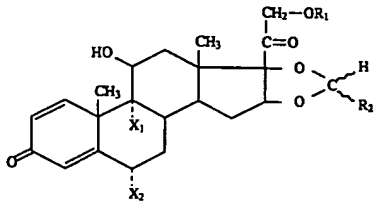
The products that are the object of the present invention have shown in the pharmacologic studies performed a low systemic effect in relation to the topical pharmacologic activity found. The difference becomes even more evident when the reference products, budesonide, flunisolide, and triamcinolone acetonide are compared; effective local pharmacologic activity and low systemic glucocorticoid response are demonstrated.

TABLE I



COMPOUND	X_1	X_2	R	IR (ester) (cm^{-1})	NMR CH_3-C (ester) δ(ppm)
1	H	H	$-COCH(CH_3)CH_3$	1720,1270	1.17(d)–1.00(d)–0.98(d)
2	F	F	$-COCH(CH_3)CH_3$	1720,1250	1.16(d)–1.07(d)–0.95(d)
3	H	F	$-COCH(CH_3)CH_3$	1730,1230	1.18(d)–1.09(d)–0.93(d)
4	H	H	$-COCH_3$	1740,1228	2.50–1.96–1.94
5	F	F	$-COCH_3$	1740,1230	2.02–2.01–1.92
6	H	F	$-COCH_3$	1740,1230	2.01–1.98–1.90

TABLE II



COMPOUND	X_1	X_2	R_1	R_2	EPIMERS	R-S PROPORTION R	S	NMR* 18-CH_3** δ(ppm)
7	H	H	$-COOCH(CH_3)CH_3$		22-R + S	40–60%	60–40%	
8	H	H	$-COCH(CH_3)CH_3$		22-S	98–99%	1–0%	0.96
9	H	H	$-COCH(CH_3)CH_3$		22-R	99.9%	0%	0.94
10	H	H	$-COCH_3$	$-CH_2-CH_2-CH_2-CH_3$	22-R + S	40–60%	60–40%	
11	H	H	$-COCH_3$	$-CH_2-CH_2-CH_2-CH_3$	22-S	99%	1%	0.97
12	H	H	$-COCH_3$	$-CH_2-CH_2-CH_2-CH_3$	22-R	99.9%	0%	0.93
13	F	F	$-COCH(CH_3)CH_3$		22-R + S	40–60%	60–40%	
14	F	F	$-COCH(CH_3)CH_3$		22-S	99–99.5%	0%	0.95
15	F	F	$-COCH(CH_3)CH_3$		22-R	99.9%	0%	0.93

*5% solution in Cl_3CD.
**Ref. TMS.

45

TABLE III

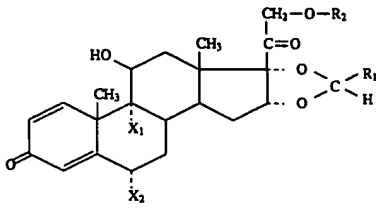
COMPOUND	EPIMER	LOCAL PHARMACOLOGIC ACTIVITY AND SYSTEMIC GLUCOCORTICOID EFFECTS EXPRESSED AS ED_{50} μg/pellet: TOPICAL ANTI-INFLAMMATORY ACTIVITY (Cotton Pellet)	SYSTEMIC GLUCOCORTICOID ACTIVITY (Thymus inhibition)	THERAPEUTIC INDEX SYSTEMIC ED_{50}/ TOPICAL ED_{50}	THERAPEUTIC INDEX WITH RESPECT TO BUDESONIDE
7	22 R,S	21.7 (17–27.7)	614.7 (279.6–1351)	28.3	26
8	22 S	20.5 (16.9–25.6)	608 (359.3–1228.3)	29.6	27.2
9	22 R	25.4 (18.2–31.1)	667.1 (321.4–1489.2)	26.2	24.5
10	22 R,S	59.9 (59.3–60.3)	583.2 (236.2–1440)	9.7	8.9
11	22 S	43 (38.4–58)	555.3 (296.3–1387.3)	12.9	11.8

TABLE III-continued

COMPOUND	EPIMER	LOCAL PHARMACOLOGIC ACTIVITY AND SYSTEMIC GLUCOCORTICOID EFFECTS EXPRESSED AS ED_{50} µg/pellet: TOPICAL ANTI-INFLAMMATORY ACTIVITY (Cotton Pellet)	SYSTEMIC GLUCOCORTICOID ACTIVITY (Thymus inhibition)	THERAPEUTIC INDEX SYSTEMIC ED_{50}/ TOPICAL ED_{50}	THERAPEUTIC INDEX WITH RESPECT TO BUDESONIDE
12	22 R	74.7 (85.3–65.1)	592.2 (265.1–1342.9)	7.9	7.2
13	22 R,S	4.5 (3.7–5.5)	54 (35–83.3)	12	11
14	22 S	3.6 (3–4.5)	49 (30.7–76.2)	13.6	15
15	22 R	5.2 (3.6–6)	56.3 (29.8–88.3)	10.8	9.9
BUDESONIDE	22 R,S	163.6 (125.1–213.9)	178.6 (81.3–392.6)	1.09	1
TRIAMCINOLONE ACETONIDE	22 R,S	220.7 (198.1–245.7)	156.4 (144.7–169)	0.7	0.6
FLUNISOLIDE	22 R,S	351.6 (268.8–459.9)	156 (188.3–224.8)	0.44	0.4

We claim:

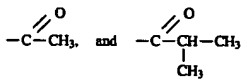
1. A compound of the formula



in the form of an R epimer, an S epimer, or a stereoisomeric mixture of the R and S epimers in terms of the orientation of the substituents on the carbon atom at position 22, wherein:

R_1 is cyclohexyl,

R_2 is a member selected from the group consisting of



and wherein X_1 and X_2 may be the same or different and each is a member selected from the group consisting of hydrogen and fluorine.

2. A compound according to claim 1 in the form of the (22S)- epimer.

3. A compound according to claim 1 in the form of the (22R)- epimer.

4. An anti-inflammatory drug containing a compound according to claim 1.

5. A method of treating inflammatory conditions which comprises administering to a patient an anti-inflammatory effective amount of a compound according to claim 1.

6. A pharmaceutical composition having anti-inflammatory properties comprising as the active ingredient an effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier.

7. A method for the treatment and control of inflammatory conditions characterized by the topical administration to a patient of an effective dose of a compound according to claim 1.

8. The compound of claim 1 which is [11β,16α(R,S)]-16,17-[cyclohexylmethylene)bis (oxy)]-11-hydroxy-21-(2-methyl- 1-oxopropoxy)pregna-1,4-diene-3,20-dione.

9. The R-epimer of the compound of claim 8.

10. The S-epimer of the compound of claim 8.

11. A compound of claim 1 wherein each of is X_1 and X_2 is hydrogen.

12. A compound of claim 1 wherein each of X_1 and X_2 is fluorine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,482,934
DATED : January 9, 1996
INVENTOR(S) : CALATAYUD ET AL

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, Item: [73] "Especialidades Latinas Medicamentos Universales, S.A. (Elmu, S.A.)" should read --Elmuquimica Farmaceutica--.

Signed and Sealed this

Third Day of February, 1998

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

EXHIBIT E

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,482,934	**$940.00**	**$0.00**	**08/278,112**	**01/09/96**	**07/20/94**	**04**	**NO**	**PAID**	**8125P57770A**

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,482,934	**$2,050.00**	**$0.00**	**08/278,112**	**01/09/96**	**07/20/94**	**08**	**NO**	**PAID**	**8125P57770A**

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EXHIBIT F

EXHIBIT F

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES [1] DURING THE REGULATORY REVIEW PERIOD FOR:

OMNARIS (ciclesonide) Nasal Spray (IND 65,488 and NDA 22-004)
And
ALVESCO (ciclesonide) Inhalation Aerosol (IND 53,391 and NDA 21-658)

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
22 Feb 2002	Meeting with FDA	Pre-IND Meeting with FDA
08 Mar 2002	Letter from FDA	FDA prepared pre-IND meeting minutes.
08 Aug 2002	**IND Submission 000 to FDA**	**INITIAL IND FILING For the use of ciclesonide nasal spray in allergic rhinitis.**
14 August 2002	Letter from FDA	Verification of receipt of IND and assignment of IND #65,488 to the project.
09 Sep 2002	Telephone contact	Inquire about IND response – no clinical hold, trials may begin
04 Oct 2002	Letter from FDA	Clinical Trials Data Bank form letter
04 Nov 2002	Letter from FDA	FDA comments to 08 Aug 2002 IND submission
02 Dec2002	IND Submission	Protocol Amendment: Change in Protocol Amendment to TBN-CL-002 to incorporate changes requested in the IND comments
10 Dec 2002	IND Submission	Info Amend: Pharm/Tox Info Amend: Clinical Response to initial IND
4 April 2003	IND Submission	General Correspondence Transfer of IND Sponsorship from Teijin America to ALTANA Pharma
8 April 2003	Telephone Contact	ALTANA informed FDA Project Manager of Sponsor transfer, contact and submission of future EOP2 meeting request
17 April 2003	Letter from FDA	Dog species for 6 month bridging study is acceptable by FDA.
20 June 2003	Telephone Contact	Provide details on Meeting Request, Request response to outstanding issues identified in S-002
23 June 2003	Telephone Contact	Dr. Anthracite of FDA stated tubular atrophy in ICF could be left to Sponsor discretion. Dr. Szema is new Medical Officer.
24 June 2003	IND Submission	Request for Formal FDA Meeting – Type B
1 July 2003	Telephone Contact	Date of Meeting: Oct 1, 2003 from 3-4:30 pm
13 Aug 2003	IND Submission	Information Amendment: Clinical Final Study Report TBN-CL-001
27 Aug 2003	IND Submission	TYPE B (EOP2) Meeting Briefing Package

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
25 Sep 2003	Letter from FDA	FDA List of Attendees
25 Sep 2003	IND Submission	General Correspondence Revised list of EOP2 attendees
01 Oct 2003	FDA Meeting	End of Phase 2 Meeting
10 Oct 2003	IND Submission	Information Amendment: Clinical Revised Pediatric Proposal in response to FDA recommendations presented at the October 1st EOP2 Meeting.
3 Nov 2003	IND Submission	Annual Report Coverage Period: 09 Sep 2002 – 08 Sep 2003
4 Nov 2003	Letter from FDA	FDA Prepared Minutes from October 1st EOP2 Meeting
24 Nov 2003	Letter from FDA	FDA Feedback to Oct 10, 2003 (S-010) Pediatric Proposal
4 Dec 2003	IND Submission	General Correspondence Request for Corrections to October 1 EOP2 Meeting Minutes (Onset of action and systemic exposure)
12 Dec 2003	IND Submission	Protocol Amendment: New Protocols BY9010\M1-401 (pivotal SAR) BY9010/M1-402 (pivotal PAR) BY9010/M1-404 (Long Term Safety)
16 Dec 2003	IND Submission	Information Amendment: Pharmacology/Toxicology SBL24-50 (Interim Report) 26 Week Intranasal Study of Ciclesonide Nasal Spray in Beagle Dogs
19 Dec 2003	IND Submission	Information Amendment: CMC Responses to Nov 4, 2002 FDA letter and updated CMC information (request for FDA feedback)
16 Jan 2004	IND Submission	General Correspondence: Protocol 401 Clinical Trial Material Provide details on an investigation and corrective action plan for clinical drug supply
30 Jan 2004	IND Submission	Information Amendment: CMC / Request for FDA feedback NDA Stability proposal
30 Mar 2004	IND Submission	Information Amendment: Clinical Statistical Analysis Plan for BY9010/M1-401
14 Apr 2004	IND Submission	Information Amendment: Clinical Final Study Report 76/2004 (Phase 2 dose range finding trial)
15 Apr 2004	IND Submission	Protocol Amendment: New Protocol Study BY9010/M1-403

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
		(Phase 3 study in children 6-11 years of age)
05 May 2004	IND Submission	Information Amendment: Clinical Revised Statistical Analysis Plan for BY9010/MI-401
27 May 2004	IND Submission	Protocol Amendment: New Protocol/Request for FDA Review and Comment Protocol BY9010/M1-405 (Phase 3 trial in children 2-5 Years of Age) Request for FDA acceptance of study design with no efficacy measurements.
10 June 2004	IND Submission	Protocol Amendment: Change in Protocol BY9010/M1-403 BY9010/M1-404
30 Jun 2004	IND Submission	General Correspondence /Request for FDA Review and Comment Submission of Clinical Pharmacology proposal: Synopses for Qvar + cic nasal and Advair + cic nasal
01 July 2004	IND Submission	Information Amendment: Clinical / Statistical Analysis Plan for BY9010-M1/402
15 July 2004	Telephone Contact	Inquire about status of review for Submission S-027 (pediatric PAR aged 2-5 years new protocol)
20 July 2004	Telephone Contact	Ms. Colette Jackson of FDA called to state that a letter has been written and requires review and approval by the Clinical Team Leader (Dr. Stark). A response is expected Friday, July 22, 2004.
27 July 2004	Letter from FDA	FDA Response to S-027 (405 trial feedback)
10 Aug 2004	Email to FDA	Request for Status of Clin Pharm proposal (S-031) and CMC stability proposal (S-018)
10 Aug 2004	IND Submission	Protocol Amendment: Change in Protocol BY9010/M1-403 Amendment 2 BY9010/M1-405 Amendment 1 version July 29, 2004 (addition of symptom assessment)
10 Aug 2004	Telephone Contact	TCON scheduled (Sept 20th 11am) for clin pharm proposal S-031 and no comment on NDA stability proposal (S-018)
31 Aug 2004	Letter from FDA	Comments regarding July 1, 2004 Serial 032 Submission (Comments to BY9010-402 SAP)
15 Sep 2004	IND Submission	General Correspondence Response to FDA comments dated 31 Aug 2004 (402 SAP)
20 Sep 2004	FDA Meeting (via teleconference)	Discussion of Clinical Pharmacology proposal
14 Oct 2004	IND Submission	Information Amendment:

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
		Pharmacology/Toxicology Toxicology reports 103/2004, 344/2003, 49/2003 , 45/2003
19 Oct 2004	Letter from FDA	FDA meeting minutes to Sep 20th TCON and comments to Clinical Pharmacology proposal
21 Oct 2004	IND Submission	Protocol Amendment: New Protocol/Change in Protocol New Protocol BY9010/406 (EEU Study) and Change in Protocol BY9010/M1-404
4 Nov2004	IND Submission	Annual Report Coverage Period 09 Sep 2003 – 08 Sep 2004
12 Nov 2004	IND Submission	Protocol Amendment: New Protocol BY9010/M1-408
07 Dec 2004	IND Submission	Protocol Amendment: New Protocol BY9010/M1-407
09 Dec 2004	IND Submission	Protocol Amendment: New Investigators/Updated Investigators
16 Dec 2004	IND Submission	Information Amendment: Clinical SAP for BY9010/M1-404
07 Jan 2005	IND Submission	Protocol Amendment: New Protocol/ Change in Protocol/ New Investigator New Protocol: BY9010/M1-409 Change in Protocol: BY9010/M1-408
17 Jan 2005	IND Submission	Information Amendment: Clinical BY9010/M1-406 SAP
18 Jan 2005	IND Submission	Protocol Amendment: Change in Protocol BY9010/M1-403 Amendment 3, version dated Dec 22, 2004
07 Feb 2005	Telephone Contact	Discuss tradename submission and eCTD submission
24 Feb 2005	IND Submission	Information Amendment: Clinical SAP for BY9010/M1-403 and -405
25 Feb 2005	Letter from FDA	Comments to S-047 (SAP for Protocol BY9010/M1-406)
02 Mar 2005	IND Submission	Protocol Amendment: Change in Protocol BY9010/M1-408 A2 + A3 BY9010/M1-409 A1
03 Mar 2005	IND Submission	Request for Type B (Pre-NDA Meeting) to discuss clinical, nonclinical, statistical and electronic format
08 Mar 2005	IND Submission	Information Amendment: Clinical SAP for BY9010/M1-408
11 Mar 2005	IND Submission	Request for Review of OPENAZE™
14 Mar 2005	Telephone Contact	Meeting Dates for Type B Meeting Request discussed with Colette Jackson
17 Mar 2005	IND Submission	Request for Type A Meeting

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
17 Mar 2005	Letter from FDA	Fax confirmation from FDA for June 7th Pre-NDA meeting date and request for 15 copies of BP
18 Mar 2005	IND Submission	Information Amendment: Clinicial SAP for BY9010/M1-406 and 407
22 Mar 2005	Telephone Contact	Call with FDA to confirm meeting date for Type A meeting. Meeting scheduled for May 9, 2005. FDA internal meeting is on 27 April 2005. Briefing Package due to FDA by 15 April 2005.
22 Mar 2005	Letter from FDA	Fax confirmation of Type A Meeting.
05 Apr 2005	Letter from FDA	Comments to Ser 053, SAP for BY9010/M1-408
11 Apr 2005	IND Submission	Information Amendment: Clinical CSR for study BY9010/M1-401 (Study report # 287/2004)
14 Apr 2005	IND Submission	Information Amendment: CMC Type A meeting Briefing Package
20 Apr 2005	IND Submission	General Correspondence Request for teleconference to discuss 408 SAP comments
22 Apr 2005	IND Submission	PRE-NDA BRIEFING PACKAGE for June 7th face to face meeting (clinical/nonclinical/e-format)
27 Apr 2005	Email correspondence	Request feedback on MedWatch requirement for postmarketing reporting
06 May 2005	Letter from FDA	FDA Comments to May 9th Type A CMC Questions regarding Micronization (briefing package submitted as serial number 059 dated 14-April 2005)
10 May 2005	Fax to FDA	Updated attendee list and dial in information for May 10 teleconference
10 May 2005	Email correspondence	FDA response to ALTANA inquiry about use of CIOMS for postmarketing safety reporting
10 May 2005	FDA Meeting (via teleconference)	Teleconference to discuss 408 SAP
11 May 2005	IND Submission	Final Study Report BY9010/M1-402
17 May 2005	Letter from FDA	SAP comments to M1-403/405
18 May 2005	Letter from FDA	FDA feedback on tradename review
19 May 2005	IND Submission	408 SAP Amendment
25 May 2005	IND Submission	Revised Datasets for Pre-NDA Meeting
26 May 2005	IND Submission	Information Amendment: Clinical Amendment to M1-405 SAP
02 June 2005	Letter from FDA	Meeting Minutes for May 10th M1-408 SAP teleconference
07 June 2005	FDA Meeting	June 7th Pre-NDA Meeting (Clinical/Nonclinical/e-format)
15 June 2005	IND Submission	Meeting Request

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
		Type B Pre-NDA (CMC)
07 July 2005	IND Submission	Protocol Amendment: Change in Protocol Amendment 2 to Protocol BY9010/M1-409
21 July 2005	IND Submission	Information Amendment: Clinical SAP for 403 (Amendment 1, version 2.0) SAP for 409 (version 1.0)
22 July 2005	Telephone Contact	Feedback on the eCTD pilot submission
29 July 2005	IND Submission	CMC Briefing Package for August 29th Type B Pre-NDA Meeting
18 Aug 2005	IND Submission	General Correspondence OPENAZE tradename rebuttal
29 Aug 2005	FDA Meeting	Pre-NDA CMC Meeting
22 Sep 2005	IND Submission	Information Amendment: Clinical SAP for 409 (Amendment 1, version 2.0)
29 Sep 2005	IND Submission	Final Study Report BY9010/M1-402
04 Oct 2005	Letter from FDA	FDA prepared CMC Pre-NDA meeting minutes (meeting held on August 29, 2005)
14 Oct 2005	IND Submission	Protocol Amendment: New Protocol BY9010/M1-416
26-Oct-2005	IND Submission	Information Amendment: Pharmacology/Toxicology Final Non-Clinical Study Reports: 29/2005, 30/2005, 151/2005, 3/2005, 4/2005, 74/2005
28-Oct-2005	28-Oct-2005	NDA Number assigned: NDA 22-004
01 Nov 2005	01 Nov 2005	OPENAZE review status and SPL requirements
04 Nov 2005	IND Submission	Annual Report Coverage Period 09 Sep 2004 – 08 Sep 2005
14 Dec 2005	Telephone Contact	Discussion on SPL requirements for Patient's Instructions for Use and Pediatric Waiver/Deferral Procedure
22 Dec 2005	IND Submission	Protocol Amendment: Change in Protocol Amendment 1, for Study BY9010/M1-416 (PAR study, 2-5 years of age
09 Jan 2006	IND Submission	Protocol Amendment: New Protocol BY9010/M1-417 (6-11 year SAR)
21 Feb 2006	Letter from FDA	Feedback on Tradename Review - OPENAZE
02 Mar 2006	IND Submission	Protocol Amendment: New Protocol BY9010/M1-412 (SAR in a park setting)
13 Mar 2006	IND Submission	Protocol Amendment: Change in Protocol Amendment 1for Study BY9010/M1-417 (6-11 year SAR)
20 Mar 2006	IND Submission	General Correspondence: Request for Comment and Advice - Feedback on proposed juvenile animal toxicology program
24 Mar 2006	IND Submission	Protocol Amendment: Change in Protocol Amendment 2for Study BY9010/M1-416 (PAR

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

IND 65,488 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
		study, 2-5 years of age).
07 Apr 2006	Letter from FDA	FDA Comments to Jan 9, 2006 BY9010/M1-417 (6-11 year SAR) and Mar 2, 2006 BY9010/M1-412 (SAR in a park setting) new protocol submissions
19 May 2006	Letter from FDA	Response to March 20, 2006 juvenile animal toxicology proposal
24 May 2006	IND Submission	Information Amendment: Clinical / Statistical Analysis Plan for BY9010-M1/416
1 June 2006	IND Submission	Protocol Amendment: Change in Protocol Amendment 2 for study BY9010/M1-417 (6-11 year SAR)
20 June 2006	IND Submission	Information Amendment: Clinical Suspension of enrollment for the 417 trial
29 June 2006	IND Submission	General Correspondence Type C Meeting Request for the VMR Indication.
14 July 2006	Letter from FDA	Type C meeting (tcon) scheduled for Sept 12, 2006 3pm.
21 July 2006	IND Submission	Protocol Amendment: New Protocol BY9010/M1-413 (EEU study)
2 Aug 2006	IND Submission	Protocol Amendment: Change in Protocol Amendment 3 Study Protocol BY9010/M1-417
10 Aug 2006	IND Submission	Type C Meeting Briefing Package - VMR
11 Aug 2006	IND Submission	Protocol Amendment: New Protocol BY9010/M1-490
7 Sept 2006	Letter from FDA	FDA responses to VMR questions for the September 12th VMR teleconference.
7 Sept 2006	Telephone contact	Discuss FDA responses to VMR and request cancellation
8 Sept 2006	IND Submission	VMR Cancellation Letter
11 September 2006	Telephone Contact	Discuss (irritant induced rhinitis indication)
19 September 2006	IND Submission	Information Amendment: Statistical Analysis Plan for BY9010/M1-417
5 October 2006	IND Submission	Protocol Amendment: Change in Protocol Amendment 1 Study Protocol BY9010/M1-490
12 October 2006	IND Submission	Information Amendment: Pharmacology/Toxicology External Nonclinical Study Report No. 261/2006

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NDA 22-004 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
21 Dec 2005	NDA Submission	New Drug Application for the use of ciclesonide nasal spray in the treatment of seasonal and perennial allergic rhinitis in patients 2 years of age and older
22 Dec 2005	Letter from FDA	NDA Fax receipt confirmation
23 Jan 2006	Telephone Contact	Respond to Med Officer inquiries and discuss OPENAZE review
10 Feb 2006	Telephone Contact	Respond to CMC reviewer (shah) on DMF for ABL 740
13 Feb 2006	Telephone Contact	Discuss outcome of NDA filing review meeting and Brandname review
20 Feb 2006	Telephone Contact	Inquiry as to whether manufacturing sites were ready for inspection. FDA was informed all sites are ready.
24 Feb 2006	Letter from FDA	NDA Acknowledgement Letter
01 Mar 2006	Telphone Contact	Discuss Brandname backup submission, an IR from the Medical Officer, and the HFA toxicology Pre-IND communication
02 Mar 2006	NDA Submission	Amendment to NDA - CMC Response to Feb 10th and 21st IRs. Submission includes Attachment to 356h – establishment info and 3.2.P.7 Container Closure System (PDP02E.000027FP/4.0)
02 Mar 2006	Letter from FDA	74-Day Communication Letter
10 Mar 2006	Telephone Contact	Information Request Colette Jackson called with a request for corrections to the LB.xpt dataset for Study 149/2005 (M1-403) and the TI.xpt dataset for Study 76/2004 (TBN-CL-002)
15 Mar 2006	Telephone Contact	Information Request from Division of Scientific Investigations 3 sites were identified for Audit: M1-405 Dr. Herron, M1-401 Dr. Freeland, Dr. Hampel. Site Information required.
17 Mar 2006	NDA Submission	Amendment to NDA – Statistical Replacement dataset for LB.xpt in Study 149/2005 (M1-403) and deletion of ti.xpt dataset for Study 76/2004 (TBN-CL-002)
17 Mar 2006	Letter from FDA	Information Request Letter CMC Comments
20 Mar 2006	Letter from FDA	Information Request Statistical Comments
21 Mar 2006	NDA Submission	Amendment to NDA – Request for Feedback Brandname review of OMNAIR and NASAIR
24 Mar 2006	NDA Submission	Amendment to NDA – CMC Response to IRs of March 2nd and 17th. Submission of LOAs to DMF 16870, DMF 12087 and DMF 11559.

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NDA 22-004 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
29 Mar 2006	Letter to FDA	Site Information Package to Div of Scientific Investigations
30 Mar 2006	NDA Submission	Amendment to NDA - Stats Response to March 20th IR for statistical information – Part I
07 Apr 2006	NDA Submission	Amendment to NDA - Stats Response to March 20th IR for statistical information – Part II
12 Apr 2006	Telephone Contact	Discuss comments from DMETS for Brandname review of OMNAIR and NASAIR
14 Apr 2006	NDA Submission	Amendment to NDA – CMC Response to Mar 17th IR. Submission includes LOA to DMF 6350 and DMF 15657. Notification of Amendment of DMF 8410 and DMF 9146. Includes, 3.2.P.7 Amendment 1 (PDP02E.000287FP/2.0)
21 Apr 2006	NDA Submission	Amendment to NDA – CMC Submission of 3.2.P.8.3 1000kg batch stability data (PSD02E.000292FP/1.0)
24 Apr 2006	Letter from FDA	Review of NDA submission and proposed proprietary names for Ciclesonide comments
04 May 2006	NDA Submission	Amendment to NDA - Clinical 4-month Safety Update Updated Proposed Labeling – Package Insert
02 Jun 2006	NDA Submission	Amendment to NDA – CMC Response to May 17 and 19 IRs. Submission includes amended 3.2.P.8.3 Stability Data for 120kg Batch Size (PSD02E.000294FP/1.0) and Executed Batch Records.
02 Jun 2006	Fax to FDA	Correspondence with Ele Pratt, FDA Division of Scientific Investigations To provide documented procedures for CRF processing in trial M1-401
06 Jun 2006	NDA Submission	Amendment to NDA – General Correspondence for Trade name Review
21 Jun 2006	NDA Submission	Amendment to NDA – General Correspondence Provide Copy of Correspondence sent to Dallas District Office regarding Dr. Herron's 483
10 Jul 2006	Telephone Contact	TCON with Colette requesting an updated amendment for the 120 kg batch data for which 12 month data was submitted in the original application.
21 Jul 2006	NDA Submission	Amendment to NDA – CMC Response to June 21 IR

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NDA 22-004 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
25 Jul 2006	NDA Submission	Amendment to NDA Response to July 14 IR Study 144/2005(M1-405) Discussion of Intraocular Pressure Data
27 Jul 2006	Letter from FDA	Discipline Review Letter Identifying deficiencies in the CMC section
02 Aug 2006	NDA Submission	Amendment to NDA – CMC Response to August 1 IR Submission of Acetaldehyde datasets for 120 and 1000kg..
04 Aug 2006	NDA Submission	Amendment to NDA Response to IR Request for SAE Listing for Ciclesonide.
06 Aug 2006	Telephone Contact	FDA requesting the SAS data sets for the 120 kg batches.
10 Aug 2006	NDA Submission	Amendment to NDA – CMC Response to July 27th and August 6th IR. Submission of datasets for micronized 18month stability data and the 120 and 1000kg primary stability batches.
11 Aug 2006	NDA Submission	Amendment to NDA – CMC Response to July 27th Discipline Review Letter.
14 Aug 2006	NDA Submission	Amendment to NDA Brandname submission of Omnaris
17 Aug 2006	NDA Submission	Amendment to NDA - CMC Response to July 10th IR for 120kg Stability Report and August 4th IR for LOA.
18 Aug 2006	NDA Submission	Amendment to NDA - CMC Response to August 17th IR for analytical procedure for leachables-aldehydes used in out of pouch stability study.
21 Aug 2006	NDA Submission	Amendment to NDA - CMC Response to August 17th IR for method validation for leachables-aldehydes used in out of pouch stability study.
22 Aug 2006	NDA Submission	Amendment to NDA Supporting safety and promotional documentation for Omnaris Brandname review.
28 Aug 2006	Telephone Contact	Discuss outcome of internal FDA review meeting, status of Brandname review, timing of the MCKO inspection, and expected timelines for receipt of the redline/strikethrough labeling.
29 Aug 2006	Telephone Contact	Agree on the regulatory test method for Leachables-aldehyde test and the stability protocol for out of pouch testing.

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NDA 22-004 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
29 Aug 2006	NDA Submission	Amendment to NDA Documented commitments regarding the Leachables-aldehydes test.
06 Sep 2006	Letter from FDA	Discipline Review Letter Identifying 14 deficiencies in the CMC section
11 Sep 2006	Telephone Contact	Discuss Submission of pediatric plans Patients instructions for use
11 Sep 2006	Telephone Contact	Revised Patient's Instructions for Use. Formal eCTD submission to follow ASAP.
13 Sep 2006	NDA Submission	Amendment to NDA - Labeling Response addressing labeling comments in the September 6, 2006 Discipline Review Letter.
15 Sep 2006	NDA Submission	Amendment to NDA - CMC Response addressing CMC comments in the September 6, 2006 Discipline Review Letter.
15 Sep 2006	Letter from FDA	Recommendations to Proposed Labeling – 1.14.1.3 Draft Labeling Text
18 Sep 2006	NDA Submission	Amendment to NDA - Labeling Response to request for carton, foil pouch, and immediate container draft labeling in actual size and color.
22 Sep 2006	NDA Submission	Amendment to NDA - Labeling Response to 15-Sep-2006 FDA recommended label
22 Sep 2006	Letter from FDA	CMC Information Request
26 Sep 2006	NDA Submission	Amendment to NDA - CMC Response to 22-Sep-2006 FDA Information Request Letter
29 Sep 2006	NDA Submission	Amendment to NDA – Labeling Response to FDA's labeling comments from September 27, 2006 telephone conference call.
04 Oct 2006	Letter from FDA	Comments to September 29th Labeling (eCTD 0030)
06 Oct 2006	NDA Submission	Amendment to NDA - Labeling Response to 04-Oct-2006 FDA Labeling comments
10 Oct 2006	NDA Submission	Amendment to NDA - Labeling Revised Trade/Physician carton reflecting peel off label and text for out of pouch expiration dating
12 Oct 2006	Letter from FDA	Comments for package components and Patient Instructions
13 Oct 2006	NDA Submission	Amendment to NDA - Labeling Response to 12-Oct-2006 FDA Draft Package Insert comments
16 Oct 2006	Letter from FDA	Postmarketing study commitment letter
16 Oct 2006	NDA Submission	Amendment to NDA - Labeling Patient's Instructions for Use and Carton, Foil Pouch, & Container Labeling.
17 Oct 2006	NDA Submission	Amendment to NDA – General Correspondence Meeting Request for Type C Meeting

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NDA 22-004 for OMNARIS (ciclesonide) Nasal Spray		
Date	**Activity**	**Comments**
18 Oct 2006	FDA Meeting (via teleconference)	Teleconference with several members of the Division to discuss the Phase IV Commitments, request for pediatric wavier, status of Brandname, and final labeling comments.
18 Oct 2006	Telephone contact	Discuss status of label comments and teleconference on Phase IV Commitments
18 Oct 2006	Letter from FDA	Assignment of Labeler Code for ALTANA Pharma US, Inc.
19 Oct 2006	Telephone Contact	To discuss Phase IV commitments with Dr Chowdhury, Dr. Lydia Gilbert-Mclain, and Colette Jackson
19 Oct 2006	NDA Submission	Phase IV Commitments, Request For Pediatric Waiver, and Revised Labeling – Package Insert, Patient's Instructions For Use and Carton and Container.
20 Oct 2006	Letters from FDA	Approval Letter for NDA 22-004 (OMNARIS approved for the use of ciclesonide in seasonal and perennial allergic rhinitis in patients 12 years of age and older) Approvable Letter for NDA 22-124 (use of ciclesonide in children 2 years to 11 years of age)

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IND 53,391 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
02-Jun-97	Initial IND Submission	Initial IND filed for the use of ciclesonide MDI in asthmatic patients
10-Jun-97	Letter from FDA	IND acknowledgement letter. IND 53,391 assigned.
03-Jul-97	IND submission	Request to Inactivate IND
15-Dec-97	**IND Submission**	**Resubmission of IND and request for reinstatement of IND. This represents the official IND submission date.**
08-Jan-98	Letter from FDA	IND acknowledgement letter.
21-Jan-98	**Telephone contact**	**"No Hold" decision given, clinical trial is authorized to begin. Official IND effective date.**
25-Mar-98	IND Submission	Protocol Amendment: Change in protocol BY9010/FK1 109
08-Sep-98	IND Submission	Nonclinical Information Amendment: 12-month oral toxicity study in dogs
18-Mar-99	Letter from FDA	3 month MDI inhalation study in dogs is sufficient instead of 6 month inhalation study in rats
19-Mar-99	IND Submission	IND ANNUAL REPORT
21-Sep-99	IND Submission	Briefing Package for End of Phase 2 Meeting
22-Oct-99	FDA Meeting	End of Phase 2 Meeting
04-Nov-99	IND Submission	Clinical Information Amendment: Clinical Study Report for Study FK1 110
15-Nov-99	IND Submission	Submission of Sponsor prepared EOP2 Meeting Minutes
24-Jan-00	FDA Meeting via Teleconference	Discuss open questions from EOP2 meeting
24-Feb-00	IND Submission	Meeting minutes from 24-Jan-00 teleconference
29-Feb-00	IND Submission	Protocol Amendment: New Protocol Study FHP 014
13-Mar-00	IND Submission	IND ANNUAL REPORT
13-Jul-00	IND Submission	Clinical Information Amendment: Bioequivalence Clinical Study Report 128/2000
17-Aug-00	IND submission	Request for Special Protocol Assessment (phase 3 and 1b protocols)
27-Sep-00	IND Submission	Request for Special Protocol Assessment (clinical pharmacology)
08-Nov-08	Email from FDA	Comments to 17-Aug-00 protocols
30-Nov-00	FDA Meeting via teleconference	Discuss FDA comments to pediatric growth study
21-Dec-00	IND Submission	Protocol Amendment: New Protocol (343 – growth effect study)
28-Dec-00	IND Submission	Minutes to 30-Nov-00 teleconference
04-Jan-01	IND Submission	CMC Amendment to support phase 3 studies
22-Jan-01	IND Submission	Request for FDA Meeting
07-Feb-01	IND Submission	Protocol Amendment: Change in Protocol (#102)
15-Feb-01	IND Submission	Briefing Package for March 9th Type B Meeting
07-Mar-01	Telephone Contact	FDA comments to Protocol 102
13-Mar-01	IND Submission	IND ANNUAL REPORT

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IND 53,391 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
13- Mar-01	IND Submission	Clinical Information Amendment: Final Report FK1 104
15-Mar-01	IND Submission	Protocol Amendment: Change in Protocol 323 and 324
20-Apr-01	IND Submission	Protocol Amendment: Change in Protocol 323
07-May-01	IND Submission	General Correspondence: Altana transferring ownership of the IND to Aventis – Effective May 9, 2001
16-May-01	IND Submission	General Correspondence: Aventis accepts ownership of IND
22-May-01	IND Submission	Protocol Amendment: New Protocol XRP1526B-341 and New Investigators
31-May-01	IND Submission	Protocol Amend.: New and Draft Protocols – XRP1526B-323LT, XRP1526B-324 LT, XRP1526B-342
21-Jun-01	IND Submission	General Corr.: Transfer of Obligations to Quintiles
28-Jun-01	IND Submission	General Corr:: Transfer of Obligations to CRO
03-Jul-01	IND Submission	Protocol Amend: New Protocol 325
18-Jul-01	IND Submission	Protocol Amend: New and Draft Protocols: 321, 322
20-Jul-01	IND Submission	Protocol Amend: New Protocol 103
03-Aug-01	IND Submission	Protocol Amend: New Protocols and Changes to Draft Protocols-341LT, 342LT
22-Aug-01	IND Submission	Protocol Amend: Change in Protocol 102
13-Sept-01	IND Submission	Authorization to Cross-Reference Letter
12-Oct-01	IND Submission	IND Safety Report - Initial
21-Dec-01	IND Submission	General Corr: Merge studies 323 and 324, which are identical in design, as one efficacy study of ciclesonide in adults and adolescents with severe persistent asthma.
14-Jan-02	IND Submission	Response to FDA Request for information
29-Jan-02	IND Submission	Protocol Amend: Change in Protocol 323, 324
31-Jan-02	IND Submission	Information Amend: CMC
01-Mar-02	IND Submission	IND Safety Report: Initial
18-Mar-02	IND Submission	Information Amend: CMC
21-Mar-02	IND Submission	Annual Report
03-Apr-02	IND Submission	Protocol Amend: Submission of a new Protocol 344
08-May-02	IND Submission	IND Safety Report - Follow-up #1: 200211633US
10-May-02	IND Submission	Response to March 7, 2002 fax from Colette Jackson
21-May-02	IND Submission	Request Pre-NDA conference with the Agency to review the status of our Clinical development program and format of CTD submission
21-May-02	IND Submission	General Correspondence: Request for Teleconference
21-May-02	IND Submission	Aventis requests a pre-NDA conference with the Agency to review status of CMC development program as well as proposed format of CTD submission.
29-May-02	IND Submission	Information Amend.: Response to FDA request to provide SAP and table of safety exposures for a proposal to combine Protocols 323 and 324 into a single efficacy study protocol
11-Jun-02	IND Submission	Protocol Amend: Amendments to Protocols' 323, 324
29-Jul-02	IND Submission	Pre-NDA Meeting Briefing Package

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IND 53,391 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
15-Aug-02	IND Submission	Information Amend: Submission of four nonclinical toxicology and toxicokinetic reports
21-Aug-02	IND Submission	Response to FDA request: FDA request that the sponsor submit a tabulated summary of all Clinical Pharmacology and Biopharmacology studies that the sponsor plans to submit in the forthcoming NDA submission.
27-Aug-02	IND Submission	Information Amend: 16 clinical study protocols (102, 103, 321, 322, 323, 324, 326, 341, 342, 344)
26-Sep-02	Telephone Contact	Contact Report: Contact Report - Follow-up Request for Information
02-Oct-02	Telephone Contact	Contact Report: Dr. Eric Floyd contacted Dr. Chowdhury to propose a Pre-IND meeting for Ciclesonide DPI Combination program and obtain concurrence on Aventis' IND filing strategy.
08-Oct-02	IND Submission	Response to FDA request: Nonclinical Toxicology and Toxicokinetic Reports
31-Oct-02	IND Submission	General Correspondence Pre-NDA Meeting Follow-up
14-Nov-02	IND Submission	Response to FDA Request: Submission of Final Statistical Analysis Plans
10-Dec-02	IND Submission	General Corr: Nonclinical Toxicology Study
02-Jan-03	IND Submission	Response to FDA Request: Executed Batch Record Documentation
15-Jan-03	IND Submission	Response to FDA Request: Response to FDA Request for Information
04-Feb-03	Telephone Contact	discuss ciclesonide MDI NDA submission.
06-Feb-03	IND Submission	Information Amend: CMC
07-Feb-03	IND Submission	Response to FDA Request: Request to the Division on details surrounding censorship of adverse events by original IND holder so that the sponsor can address these concerns.
21-Feb-03	IND Submission	Response to FDA Request: Unequivocal confirmation that no censorship of safety data has occurred in the Altana database at any point during the clinical development of ciclesonide MDI.
04-Mar-03	IND Submission	Response to FDA Request: final Statistical Analysis plan for Protocol 342 (persistent asthma in children).
10-Mar-03	IND Submission	Information Amend: CMC information amendment submission provides updated information on the CMC for the drug substance and drug product
21-Mar-03	IND Submission	ANNUAL REPORT
16-Apr-03	IND Submission	Response to FDA request: Statistical Analysis Plan
21-Apr-03	IND Submission	Response to FDA request: Pathology Working Group Report on Dog Testes.

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IND 53,391 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
28-Apr-03	IND Submission	General Corr: Request for Type C Meeting with the Agency to review preliminary safety data from our pivotal clinical studies.
05-May-03	IND Submission	General Corr: Dose Counter Specifications
16-May-03	IND Submission	Information Amend: Serial No. 189 replaced Serial No. 188 (original number on document) per authorization by Daniel Bollag.Reference is made to 4/28/03 Request for Type C Meeting and to telephone conversation. Aventis is submitting a background package for the June 2 meeting.
22-May-03	IND Submission	General Corr: Serial No. 190 (changed from 189) Medical Officer Review of a 473 patient efficacy and safey study
24-Jun-03	IND Submission	General Corr: new drug application field copy submission
24-Jun-03	IND Submission	Type A meeting request
01-Jul-03	IND Submission	General Corr: allow for the cross-reference of any information submitted to IND 53,391 for ciclesonide MDI. Responsibility for IND 65,488 for ciclesonide nasal spray was transferred from Teijin America, Inc. to the following sponsor on April 4, 2003: ALTANA Pharma.
17-Jul-03	IND Submission	Information Amendment: Background package for the August 7 meeting
21-Jul-03	IND Submission	General Corr: request for concurrence from the FDA about appropriate specification ranges for the dose counter being developed as part of the metered dose inhaler device.
13-Aug-03	IND Submission	General Corr: Sponsor prepared meeting minutes from the August 7, 2003 meeting.
14-Aug-03	IND Submission	Information Amend: draft study protocol SRP 1526B-3027
11-Sep-03	IND Submission	General Corr: Request for concurrence from FDA concerning clinical dataset and SAS program submission plans.
14-Oct-03	IND Submission	General Corr: Response to FDA Protocol Review
31-Oct-03	IND Submission	Information Amend: CMC
22-Dec-03	**Original NDA Submission**	**NDA Original Submission for ciclesonide MDI**
26-Dec-03	IND Submission	Protocol Amend: New Protocol 3027
19-Mar-04	IND Submission	ANNUAL REPORT
07-Apr-04	IND Submission	General Corr.: Transfer of certain IND responsibilities to PPD, a contract research organization.
07-Apr-04	IND Submission	General Corr: Transfer of certain IND responsibilities to MMATISS, a contract research organization.

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IND 53,391 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
07-Apr-04	IND Submission	General Corr: Transfer of certain IND responsibilities to Pharm-Olam International, a contract research organization
14-May-04	IND Submission	General Corr: Transfer of certain IND responsibilities to PPD, a contract research organization.
08-Jun-04	FDA Teleconference	Contact Report: This teleconference was arranged as a Type A meeting to discuss comparator supply issues in the ongoing clinical study #3027 to evaluate lens opacification.
06-Jul-04	IND Submission	Response to FDA request: chemistry protocol outline to compare QVAR metered dose inhalers obtained outside of the U.S. with QVAR devices sourced in the U.S.
07-Jul-04	IND Submission	General Corr: Transfer of certain IND responsibilities to Quintiles, a contract research organization.
07-Jul-04	IND Submission	Information Amend: Pharmacology/Toxicology
13-Sep-04	IND Submission	Information Amendment: Chemistry Protocol Amendment: New Protocol
29-Oct-04	IND Submission	Information Amendment: final Statistical Analysis plan for Protocol 343
02-Dec-04	IND Submission	Protocol Amendment - Change in Protocol Protocol XRP1526B/3027 - Amendment #2
01-Feb-05	IND Submission	Protocol Amendment – New Protocol(XRP1526B/3028)
11-Mar-05	IND Submission	IND ANNUAL REPORT: Annual report summarizes the progress of investigations from January 21, 2004 to January 20, 2005.
15-Mar-05	IND Submission	IND Safety Report: Follow-up
01-Apr-05	IND Submission	Protocol Amend: New Protocols: 3030 & 3031
29-Jun-05	IND Submission	Protocol Amendment - Change in Protocol XRP1526B/3027.
12-Jul-05	IND Submission	Information Amend: final study report for protocol XRP1526B-343, dated June 9, 2005.
01-Aug-05	IND Submission	Information Amendment - Clinical Statistical Analysis Plan
18-Nov-05	IND Submission	Information Amendments-Clinical-3028
12-Dec-05	IND Submission	Protocol Amendments-Change in Protocol Protocol No.: XRP1526B/3031
22-Dec-05	IND Submission	Information Amendment-Clinical XRP1526B/3027 Final Study Report
30- Jan-06	IND Submission	General Corr: Transfer of Responsibility to PPD. Reference made to following protocols: XRP1526B/3028, XRP1526B/3030, XRP1526B/3031 transferred specific regulatory responsibilities for these clinical studies to PPD Development/Morrisville, NC.
01- Mar-06	IND Submission	Information Amendment: CMC
17-Mar-06	IND Submission	ANNUAL REPORT covering period January 21, 2005 to January 20, 2006

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IND 53,391 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
06-Apr-06	IND Submission	Information Amendments - Clinical Protocol No. XRP1526/3031 (submitted April 1, 2005, Serial No. 235)
21-Apr-06	IND Submission	Information Amendments- Clinical. Protocol No. XRP1526/3030
26-Apr-06	IND Submission	Information Amendment - Clinical; Statistical Analysis Plan for protocol XRP1526B/3030.
25-May-06	IND Submission	Protocol Amendment-New Protocol
19-Jun-06	IND Submission	Information Amendment - Clinical, Statistical Analysis Plan for protocol XRP1526B/3028
27-Jun-06	IND Submission	Protocol Amendment - Request for Special Protocol Assessment for clinical protocol XRP1526B/EFC6695.
12-Jul-06	IND Submission	Information Amendment: CMC - drug substance and drug product sections are updated to include 36-month stability data.
13-Jul-06	IND Submission	General Correspondence - providing verification that the drug substance and drug product referenced in IND 53,391 are the same as that referenced in NDA 21-658.
03-Aug-06	IND Submission	General Corr: authorization for FDA to access any information in the IND 53,391 (ciclesonide metered dose inhaler) or NDA 21-658 (Alvesco, ciclesonide metered dose inhaler) for the review of the planned submission for ciclesonide HFA nasal spray (IND 74,674) sponsored by: Altana Pharma US Inc.
09-Oct-06	IND Submission	Information Amend: correspondence regarding protocol XRP1526B/EFC6695
19-Oct-06	IND Submission	General Corr: Request for advice on proposed embossments on the MDI device.

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NDA 21-658 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
22-Dec-03	Original NDA Submission	NDA Original Submission for ciclesonide MDI
22-Jan-04	Letter from FDA via facsimile	NDA Acknowledgement Letter
23-Jan-04 27-Jan-04	Telephone Contact	Division of Scientific Investigations called to request information regarding clinical site audits
05-Feb-05	NDA Submission	Format modifications to NDA
10-Feb-05	Telephone Contact	FDA request for program code and data files for studies DMPK US/01-0185 and DMPK 2003/0019
18, 19, 20, 23-Feb-04	Telephone Contact	Various CMC requests for information (stability data sets, expiry dating calculations, methods validation)
02-Mar-04	NDA Submission	Response to request for SAS datasets
04-Mar-04	NDA Submission	Response to CMC request for methods validation
10-Mar-04	NDA Submission	SAS data sets for content assay
08-Mar-04	Letter from FDA via facsimile	Notification that NDA has been filed under section 505(b) of the Act on February 21, 2004 in accordance with 21 CFR 314.101(a)
22-Mar-04	NDA Submission	Response to Pediatric requirements, request for partial waiver in children younger than 6 months of age.
02-Apr-04	NDA Submission	Aventis response to questions identified in the filing review letter
26-Apr-04	NDA Submission	120 Day Safety Update Report
29-Apr-04	NDA Submission	Response to 08-Mar-04 Filing Review letter (CMC)
27-May-04	NDA Submission	Response to FDA request for information: Pediatric drug development plans
10-Jun-04	Letter from FDA via facsimile	Comments and Information request regarding CMC
08-Jul-04	Letter from FDA via facsimile	Clinical Information Request : Biopharm questions
04-Aug-04	NDA Submission	Response to 08-Jul-04 Information Request
22-Sep-04	NDA Submission	CMC: Methods validation package for ciclesonide drug substance
27-Sep-04	NDA Submission	CMC: Drug Master File 12,464 amended by DMF holder
27-Sep-04	NDA Submission	CMC response to FDA request for information
01-Oct-04	Letter from FDA via facsimile	FDA approval of March 22, 2004 partial waiver request for pediatric studies in patients zero to less than 6 months of age
06-Oct-04	Teleconference	Teleconference with FDA to discuss adult once-daily indication, stratum analysis, pediatric studies and HPA-axis data

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.

NDA 21-658 for ALVESCO (ciclesonide) Metered Dose Inhaler		
Date	**Activity**	**Comments**
21-Oct-04	Action Letter	**FDA Approvable Letter**
25-Oct-04	NDA Submission	Response to 21-Oct-04 FDA Action Letter
03-Dec-04	FDA Meeting - Teleconference	FDA Meeting to discuss deficiencies identified within the 21-Oct-04 Approvable Letter
18-Jul-05	FDA Meeting – Teleconference	FDA Meeting to discuss approval of ALVESCO for asthma in children 4 to 11 years of age.
26-Jul-05	FDA Meeting – Teleconference	FDA Meeting to discuss CMC topics
07-Feb-06	NDA Submission	Request for advice on proposed format of clinical data to be submitted in response to the 21-Oct-04 approvable letter
21-Mar-06	FDA Letter via facsimile	FDA response to 07-feb-06 request for advice

[1] Submissions of Safety Reports under 21 C.F.R. § 312.32 and additional investigators to various protocols occurred at various times throughout the Regulatory Review Period.